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(71) Applicants (for all designated States except US): TANABE SEIYAKU CO., LTD. [JP/JP]; 2-10, Dosho-Machi 3-chome, Chuo-ku, Osaka 541-8505 (JP). PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LOBL, Thomas J. [US/US]; Coulter Pharmaceutical, Suite 200, 550 California Avenue, Palo Alto, CA 94306 (US). RISHTON, Gil [US/US]; Amgen, 1840 DeHavilland Drive, Thousand Oaks, CA 91320-1789 (US). TEEGARDEN, Bradley [US/US]; 11933 Windom Parkway, San Diego, CA 92131 (US). POLINSKY, Alex [US/US]; Alanex Corporation, 3550 General Atomics Court, San Diego, CA 92121-1122 (US). YAMAGISHI, Masafumi [JP/JP]; 5-186-2-1501, Showadori, Amagasaki-shi, Hyogo-ken 660-0881 (JP). TANIS, Steven, P. [US/US]; 7601 Farmington Avenue, Kalamazoo, MI 49002 (US). FISHER, Jed, F. [US/US];			
(54) Title: INHIBITORS OF $\alpha_4\beta_1$ MEDIATED CELL ADHESION			
(57) Abstract			
The present invention relates to small molecules according to formula (I), which are potent inhibitors of $\alpha_4\beta_1$ mediated adhesion to either VCAM or CS-1 and which can be used for treating or preventing $\alpha_4\beta_1$ adhesion mediated conditions in a mammal such as a human.		<p style="text-align: right;">(I)</p>	

INHIBITORS OF $\alpha_4\beta_1$ MEDIATED CELL ADHESIONBACKGROUND OF THE INVENTIONField of the Invention

5 The present invention relates to small molecules that are potent inhibitors of $\alpha_4\beta_1$ mediated adhesion to either VCAM or CS-1 and which could be useful for the treatment of inflammatory diseases.

Description of Related Art

10 The extracellular matrix (ECM) is the major component of connective tissue which provides structural integrity, and promotes cell migration and differentiation. As part of these functions, extracellular matrix molecules such as fibronectin, collagen, laminin, von Willebrand factor, 15 thrombospondin, fibrinogen, and tenascin have been shown to support adhesion of cells in vitro. This adhesive interaction is critical for a number of biological processes including hemostasis, thrombosis, wound healing, tumor metastasis, immunity and inflammation.

20 Fibronectin (FN) is the prototype ECM molecule. The major cell attachment site in the fibronectin molecule has been reproduced synthetically with the amino acid sequence arginine-glycine-aspartic acid, or RGD using single letter nomenclature. Peptides 25 containing the RGD sequence which either inhibit or promote cell adhesion have been described (US Patent Nos. 4,589,881; 4,661,111; 4,517,686; 4,683,291;

4,578,079; 4,614,517; and 4,792,525). Changes in the peptide as small as the exchange of alanine for glycine or glutamic acid for aspartic acid, which constitute the addition of a single methyl or methylene group to the tripeptide, eliminates these activities (Pierschbacher et al., *Proc. Natl. Acad. Sci. USA* 81:5985 (1984)). Recently, a second FN cell binding domain has been identified within the alternatively spliced region of the A chain of the molecule, known as the connecting segment 1 (CS-1). The most active cell-binding site within this alternatively spliced region is composed of 25 amino acids where the carboxy terminus contains the sequence EILDVPST. The amino acid sequence EILDVPST forms a recognition motif on FN for cell surface receptors. (Wayner et al., *J. Cell Biol.* 109:1321 (1989); Guan et al., *Cell* 60:53 (1990)).

The receptors which recognize these sites on FN belong to a gene superfamily called integrins which consist of heterodimeric complexes of non-covalently associated alpha and beta subunits. A common β subunit combines with unique α subunits to form an adhesion receptor of defined specificity. To date, 8 β subunits have been identified which can dimerize with 16 distinct α subunits forming 22 distinct integrins. The β 1 subfamily, also known as the VLA family (Very Late Activation Antigens), binds to ECM molecules such as FN, collagen and laminin. For reviews, see, Hynes, *Cell* 48:549 (1987); Hemler, *Annu. Rev. Immunol.* 8:365 (1990). Leukocyte interaction with FN at the two spatially separate binding domains is mediated by two distinct integrins. The RGD site is recognized by the integrin $\alpha_5\beta_1$, while, EILDV is recognized by $\alpha_4\beta_1$ (Pytela et al., *Cell* 40:191 (1985); Wayner et al., *J. Cell Biol.* 109:1321 (1989); Guan et al., *Cell* 60:53 (1990)).

Vascular endothelial cells form the interface between blood and tissues and control the passage of leukocytes as well as plasma fluid into tissues. A

variety of signals generated at the site of inflammation can activate both endothelial cells as well as circulating leukocytes so that they become more adhesive to one another. Following this initial adhesion the
5 leukocytes migrate into the tissues to perform host defense functions. Several adhesion molecules have been identified which are involved in leukocyte-endothelial interactions.

In the β_1 subfamily, in addition to binding to
10 fibronectin, $\alpha_4\beta_1$ interacts with a cytokine inducible protein on endothelial cells termed vascular cell adhesion molecule (VCAM). Further involved in the leukocyte-endothelial adhesion process is the β_2 integrin subfamily. β_2 integrins include CD11a/CD18, CD11b/CD18,
15 and CD11c/CD18. In addition, the β_7 subunit associates with α_4 to form a unique $\alpha_4\beta_7$ heterodimer which binds to FN, to VCAM, and to Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM) (Ruegg et al, *J. Cell.Biol.* 117:179 (1992); Andrew et al., *J. Immunol.* 153:3847 (1994);
20 Briskin et al., *Nature* 363:461 (1993); Shyjan et al, *J. Immunol.* 156:2851 (1996)). α_4 integrins are widely expressed on different cell types including hematopoietic progenitors, lymphocytes, natural killer cells, monocytes, eosinophils, basophils, and mast cells
25 (Helmer, M. E., *Annu. Rev. Immunol.* 8:365 (1990)). Other molecules on endothelial cells which bind to the leukocytes include ICAM-1, ICAM-2, E-selectin and P-selectin (Carlos and Harlan, *Immunol. Rev.* 114:1 (1990); Osborn, L., *Cell* 62:3 (1990); Springer T.,
30 *Nature* 346:425 (1990); Geng et al., *Nature* 347:757 (1990); Stoolman, *Cell* 56:907 (1989)).

A number of *in vitro* and *in vivo* studies indicate that $\alpha_4\beta_1$ plays a critical role in the pathogenesis of a variety of diseases. Monoclonal antibodies directed
35 against α_4 have been tested in a variety of disease models. Anti- α_4 antibodies block adhesion of lymphocytes to synovial endothelial cells; this adhesion plays a

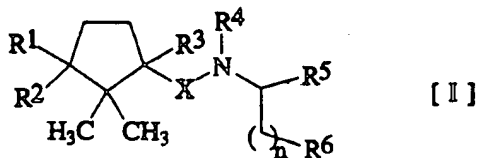
potential role in rheumatoid arthritis (van Dinther-Janssen et al, *J. Immunol.* 147:4207 (1991)). α_4 has also been implicated with respect to rheumatoid arthritis in separate studies (Laffon et al, *J. Clin. Invest.* 88:546
5 (1991); Morales-Ducet et al, *J. Immunol.* 149:1424 (1992)). A significant number of studies have evaluated the role of α_4 in allergy and asthma. For example, monoclonal antibodies to α_4 block adhesion of basophils and eosinophils to cytokine activated endothelial cells
10 (Walsh et al, *J. Immunol.* 146:3419 (1991); Bochner et al, *J. Exp. Med.* 173:1553 (1991)). Monoclonal antibodies to α_4 were also effective in several lung antigen challenge models (Abraham et al, *J. Clin. Invest.* 93:776 (1994); Weg et al, *J. Exp. Med.* 177:561
15 (1993)). The cotton-top tamarin, which experiences spontaneous chronic colitis, showed a significant attenuation of their colitis when anti- α_4 antibody was administered (Podolsky et al, *J. Clin. Invest.* 92:372 (1993); Bell et al, *J. Immunol.* 151:4790 (1993)). In a
20 rat and mouse model, autoimmune encephalomyelitis was blocked by anti- α_4 antibody (Yednock et al, *Nature* 356:63 (1992); Baron et al, *J. Exp. Med.* 177:57 (1993)). Anti- α_4 monoclonal antibodies also inhibit insulinitis and delay the onset of diabetes in the non-obese diabetic
25 mouse (Baron et al, *J. Clin. Invest.* 93:1700 (1994); Yang et al, *Proc. Natl. Acad. Sci. USA* 90:10494 (1993); Burkly et al, *Diabetes* 43:529 (1994)). α_4 is also implicated in atherosclerosis due to its endothelial expression during atherogenesis (Cybulsky et al, *Science*
30 251:788 (1991)). The migration of leukocytes to an inflammatory site can also be blocked by anti- α_4 antibodies. In addition to the blocking of migration, inhibitors of leukocyte endothelial adhesion may block the costimulatory signals mediated by integrins and thus
35 inhibit overproduction of inflammatory cytokines. In a separate set of experiments not using anti- α_4 antibodies, the peptides GRDGSP or EILDV were tested against contact

hypersensitivity response. The contact hypersensitivity response was found to be blocked by GRDGSP or EILDV suggesting that both $\alpha_4\beta_1$ and $\alpha_5\beta_1$ are involved in this inflammatory response.

5 Other ailments which may involve $\alpha_4\beta_1$ -mediated conditions include the inflammatory disorders rheumatoid arthritis, allergic disorders, asthma, spontaneous chronic colitis, insulinitis, contact hypersensitivity response, atherosclerosis and autoimmune
10 encephalomyelitis. These studies illustrate that small molecules that are potent inhibitors of $\alpha_4\beta_1$ mediated adhesion to either VCAM-1 or CS-1 may be used as a form of treatment in numerous inflammatory diseases. However, these inflammatory conditions could be expanded
15 to include adult respiratory distress syndrome, AIDS, cardiovascular diseases, thrombosis or harmful platelet aggregation, reocclusion following thrombolysis, allograft rejection, reperfusion injury, psoriasis, eczema, contact dermatitis and other skin inflammatory
20 diseases, osteoporosis, osteoarthritis, atherosclerosis, neoplastic diseases including metastasis of neoplastic or cancerous growth, wound healing enhancement, treatment of certain eye diseases such as detaching retina, Type I diabetes, multiple sclerosis, systemic
25 lupus erythematosus (SLE), inflammatory and immunoinflammatory conditions including ophthalmic inflammatory conditions and inflammatory bowel diseases, ulcerative colitis, regional enteritis and other autoimmune diseases. Accordingly, a compound which
30 could inhibit these conditions is desirable.

SUMMARY OF THE INVENTION

The present invention is directed to a compound of the formula [I]:

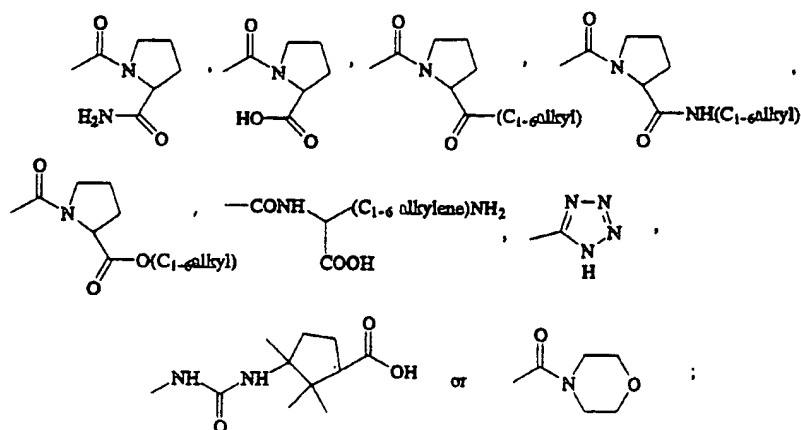


In the above formula [I], n is an integer of 0 or 1, R¹ is a hydrogen atom or a methyl group, and R² can be selected from the following: a -CN group; a -COOH group; a -(C₁₋₆ alkylene)OH group, preferably a -(C₁₋₃ alkylene)OH group; a CH₂O(C₁₋₆ alkyl) group, preferably a -CH₂O(C₁₋₃ alkyl) group; a -(C₁₋₃ alkylene)COOH group, preferably a -(C₁₋₃ alkylene)COOH group; a -CH₂O(C₁₋₆ alkylene)O(C₁₋₆ alkyl) group, preferably a -CH₂O(C₁₋₃ alkylene)O(C₁₋₆ alkyl) group or a -CH₂O(C₁₋₆ alkylene)O(C₁₋₃ alkyl) group, more preferably a -CH₂O(C₁₋₃ alkylene)O(C₁₋₃ alkyl) group; a -CH₂O(C₁₋₆ alkylene)COOH group, preferably a -CH₂O(C₁₋₃ alkylene)COOH group; a -(C₂₋₇ alkenylene)COOH group, preferably a -(C₂₋₄ alkenylene)COOH group; a -CO(C₁₋₆ alkylene)COOH group, preferably a -CO(C₁₋₃ alkylene)COOH group; a -CO(C₂₋₇ alkenylene)COOH group, preferably a -CO(C₂₋₄ alkenylene)COOH group; a -CO(C₁₋₆ alkylene)O(C₁₋₆ alkyl) group, preferably a -CO(C₁₋₃ alkylene)O(C₁₋₆ alkyl) group or a -CO(C₁₋₆ alkylene)O(C₁₋₃ alkyl) group, more preferably a -CO(C₁₋₃ alkylene)O(C₁₋₃ alkyl) group; a -CO(C₁₋₆ alkylene)CO(C₁₋₆ alkyl) group, preferably a -CO(C₁₋₃ alkylene)CO(C₁₋₆ alkyl) group or a -CO(C₁₋₆ alkylene)CO(C₁₋₃ alkyl) group, more preferably a -CO(C₁₋₃ alkylene)CO(C₁₋₃ alkyl) group; a -CONH(C₁₋₆ alkyl) group, preferably a -CONH(C₁₋₃ alkyl) group; a -CONHO(C₁₋₆ alkyl) group, preferably a -CONHO(C₁₋₃ alkyl) group; a -CONH(C₁₋₆ alkylene)COOH group, preferably a -CONH(C₁₋₃ alkylene)COOH group, a -CONH₂ group; a -CONH(C₃₋₇ cycloalkyl) group, preferably a -CONH(C₃₋₆ cycloalkyl) group; a group as follows:



a -CONHOCH₂Ph group; a -CONH(C₁₋₆ alkylene)CN group, preferably a -CONH(C₁₋₃ alkylene)CN group; a -COO(C₁₋₆ alkyl) group, preferably a -COO(C₁₋₃ alkyl) group; a -CH₂O(C₁₋₆ alkylene)CONH₂ group, preferably a -CH₂O(C₁₋₃ alkylene)CONH₂ group; a -CONH(C₁₋₆ alkylene)CONH₂ group,

preferably a $-\text{CONH}(\text{C}_{1,3} \text{ alkylene})\text{CONH}_2$ group; a $-\text{CONHOH}$ group; a $-\text{NHCooCH}_2\text{Ph}$ group; or a group selected from the following formula:

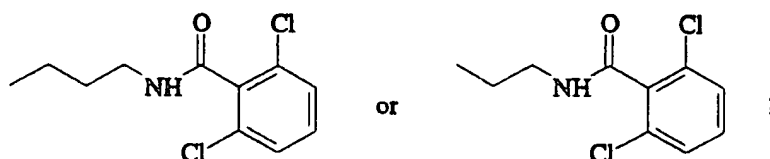


In the above Formula (I), in R^2 , the $\text{C}_{1,6}$ alkylene is preferably $\text{C}_{1,3}$ alkylene, the $\text{C}_{2,7}$ alkenylene is preferably $\text{C}_{2,4}$ alkenylene, the $\text{C}_{1,6}$ alkyl is preferably $\text{C}_{1,3}$ alkyl and the $\text{C}_{3,7}$ cycloalkyl is preferably $\text{C}_{3,6}$ cycloalkyl.

In the above formula [I], R^3 can be a hydrogen atom or a methyl group, X can be a methylene group or a $-\text{CO}-$ group, and R^4 can be selected from the following: a hydrogen atom; or a $\text{C}_{1,6}$ alkyl group, preferably a $\text{C}_{1,3}$ alkyl group.

In the above formula [I], R^5 can be a group selected from the following: a $-\text{COOH}$ group or an ester or an amide thereof; a $-(\text{C}_{1,6} \text{ alkylene})\text{COOH}$ group, preferably a $-(\text{C}_{1,3} \text{ alkylene})\text{COOH}$ group, or an ester or an amide thereof; a $-(\text{C}_{1,7} \text{ alkylene})\text{O}(\text{C}_{1,6} \text{ alkyl})$ group, preferably a $-(\text{C}_{1,4} \text{ alkylene})\text{O}(\text{C}_{1,6} \text{ alkyl})$ group or a $-(\text{C}_{1,7} \text{ alkylene})\text{O}(\text{C}_{1,3} \text{ alkyl})$ group, more preferably a $-(\text{C}_{1,4} \text{ alkylene})\text{O}(\text{C}_{1,3} \text{ alkyl})$ group; a $-(\text{C}_{1,7} \text{ alkylene})\text{OH}$ group, preferably a $-(\text{C}_{1,4} \text{ alkylene})\text{OH}$ group; a $-\text{COO}(\text{C}_{1,6} \text{ alkyl})$ group, preferably a $-\text{COO}(\text{C}_{1,3} \text{ alkyl})$ group; a $-\text{CONH}(\text{C}_{1,6} \text{ alkyl})$ group, preferably a $-\text{CONH}(\text{C}_{1,3} \text{ alkyl})$ group; or a $-\text{CONH}_2$ group.

In the above formula [I], R^6 can be a substituted or unsubstituted monocyclic or bicyclic aryl group, a substituted or unsubstituted monocyclic or bicyclic heteroaryl group, a substituted or unsubstituted monocyclic or bicyclic arylcarbonylamino- C_{1-6} alkyl group, a substituted or unsubstituted monocyclic or bicyclic aliphatic heterocyclic carbonyl group, a 9-fluorenylmethyloxycarbonylamino- C_{1-6} alkyl group, a 3-tosylguanidino- C_{1-6} alkyl group,



provided that R^1 and R^3 must be different and when R^2 or R^6 is a -COOH group or contains a -COOH group, then a pharmaceutically acceptable ester or a pharmaceutically acceptable amide thereof are included and also with the proviso that [1S-[1 α , (R^*), 3 α]]- α -[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-4-(2,6-dichlorobenzoyl)- γ -oxo-1-pyrazinebutanoic acid methyl ester or [1S-[1 α , (R^*), 3 α]]- β -[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-4-(2,6-dichlorobenzoyl)- γ -oxo-1-pyrazinebutanoic acid methyl ester are excluded.

In the above formula [I], in R^6 , an aryl group or aryl moiety in the arylcarbonylamino group is a 5- or 6-membered aromatic hydrocarbon ring; and including any bicyclic group in which any of the above ring is fused to another above ring; and substituted by zero (0) to three (3) substituents.

Examples of aryl can include phenyl, a C_{1-6} alkoxyphenyl group and naphthyl group. Each of these moieties may be substituted as appropriate.

In R⁶, a heteroaryl is a 5- or 6-membered partially saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C₃-C₈ cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) substituents.

Examples of heteroaryl can include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxaliny, 1-phthalazinyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuryl, 3-benzofuryl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 1,2,4-oxadiazolyl-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl. Each of these moieties may be substituted as appropriate.

In R⁶, an aliphatic heterocyclic moiety in aliphatic heterocyclic carbonyl group is a 5- or 6-membered saturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is

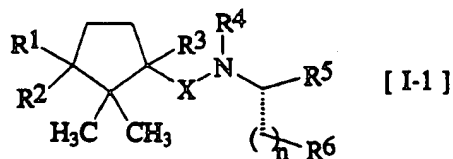
fused to a benzene ring, C₃-C₈ cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) substituents.

5 Examples of aliphatic heterocyclic can include piperazinyl group, pyrrolidinyl group, piperidyl group, homopiperidyl group, thiomorpholino group, and morpholino group. Each of these moieties may be substituted as appropriate.

10 According to the present invention, the term "C₁₋₆ alkyl" represents an alkyl group having 1 to 6 carbon atoms. This group may be straight or branched. Illustrative but non-limiting examples of a C₁₋₆ alkyl group are methyl, ethyl, n-propyl, isopropyl, n-butyl, 15 iso-butyl, tert-butyl, sec-butyl, n-pentyl, isopentyl and n-hexyl. It is understood that this type of nomenclature extends to terms such as "C₁₋₆ methoxy" and therefore encompasses both straight and branched methoxy groups having 1 to 6 carbon atoms.

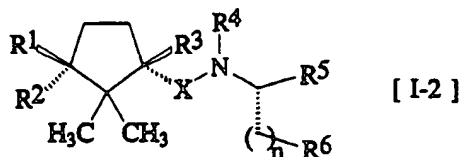
20 Also, in the above formula [I] with all substituents as described above, a pharmaceutically acceptable salt thereof is included.

The desired compounds of the present invention have preferred steric configurations. Accordingly, a preferred steric configuration is represented by 25 compounds of the formula [I-1]:



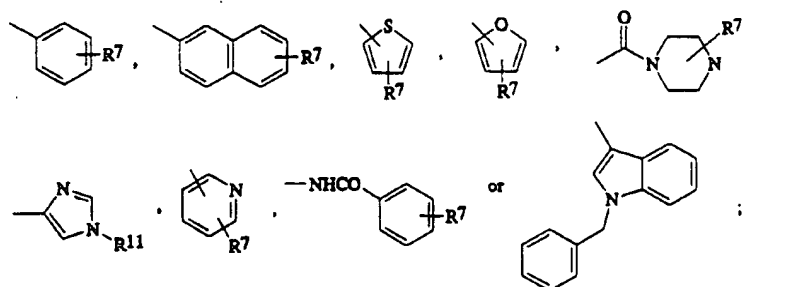
wherein n, R¹ through R⁶ and X are as defined above.

A more preferred steric configuration is represented by compounds according to the formula [I-2]:



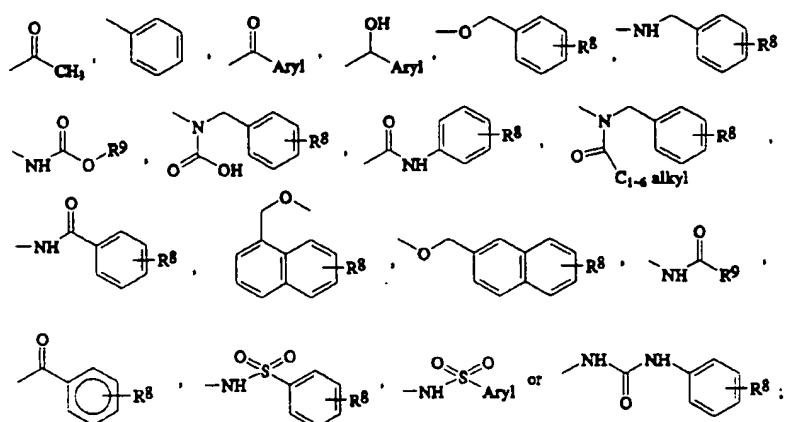
wherein n, R¹ through R⁴, R⁶ and X are as defined above and R⁵ can be selected from the following: a -COOH group; a -(C₁₋₆ alkylene)COOH group, preferably a -(C₁₋₃ alkylene)COOH group; a -(C₁₋₇ alkylene)O(C₁₋₆ alkyl) group, preferably a -(C₁₋₄ alkylene)O(C₁₋₆ alkyl) group or a -(C₁₋₇ alkylene)O(C₁₋₃ alkyl) group, more preferably a -(C₁₋₄ alkylene)O(C₁₋₃ alkyl) group; a -(C₁₋₇ alkylene)OH group, preferably a -(C₁₋₄ alkylene)OH group; a -COO(C₁₋₆ alkyl) group, preferably a -COO(C₁₋₃ alkyl) group; a -CONH(C₁₋₆ alkyl) group, preferably a -CONH(C₁₋₃ alkyl) group or a -CONH₂ group.

In a preferred embodiment of the present invention, R⁶ can be selected from the following formula:



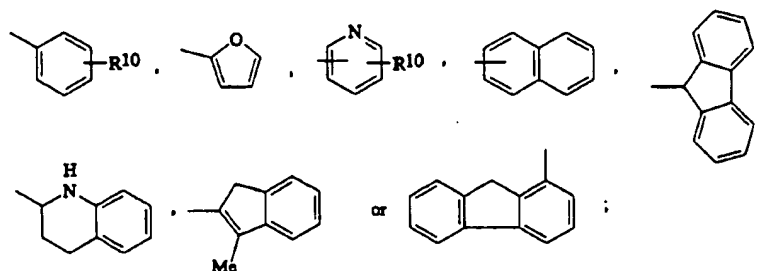
In the above, R⁷, which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -OH group; a -NO₂ group; a -NH₂ group; a -C₁₋₅ alkyl group, preferably a -C₁₋₃ alkyl group; a -F group; a -Cl group; a -Br group; a -I group; a -COOH group; a -COO(C₁₋₆ alkyl) group, preferably a -COO(C₁₋₃ alkyl) group; a -O(C₁₋₆ alkyl) group, preferably a -O(C₁₋₄ alkyl) group; a -

CONH(C₁₋₆ alkylene)COOH group, preferably a -CONH(C₁₋₃ alkylene)COOH group; a -OCH₂(C₃₋₇ cycloalkyl) group, preferably a -OCH₂(C₃₋₆ cycloalkyl) group; or a substituent selected from the following formula:



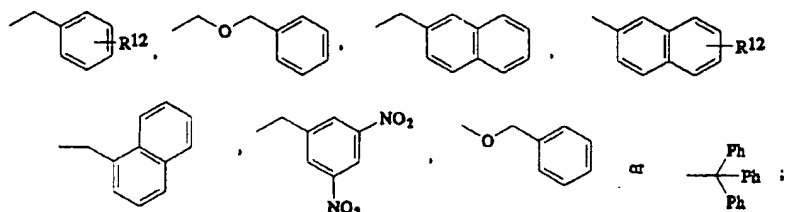
- 5 In the above, R⁸, which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; an -OH group; a -NH₂ group; a -NO₂ group; a -C₁₋₇ alkyl group, preferably a -C₁₋₄ alkyl group; a -F group; a -Cl group; 10 a -Br group; a -I group; a -CF₃ group; a phenyl group, or a -O(C₁₋₆ alkyl) group, preferably a -O(C₁₋₃ alkyl) group.

- In the above, R⁹ may be selected from the following: a -H group; a -C₁₋₅ alkyl group, preferably a -C₁₋₃ alkyl group; a -C₃₋₇ cycloalkyl group, preferably a -C₃₋₆ 15 cycloalkyl group; a -(C₁₋₆ alkylene)aryl group, preferably a -(C₁₋₃ alkylene)aryl group; an aryl group; or a group selected from the following formula:



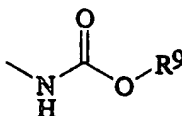
In the above, R^{10} , which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -F group; a -Cl group; a -Br group; an -I group; a -NO₂ group; a -C₁₋₆ alkyl group, preferably a -C₁₋₃ alkyl group; or a -O(C₁₋₆ alkyl) group, preferably a -O(C₁₋₃ alkyl) group.

In the above, R^{11} may be selected from the following:



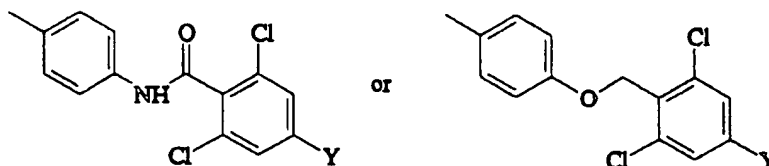
In the above, R^{12} , which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -CF₃ group; a -OCH₃ group; a -F group; a -Br group; a -Cl group; or an -I group;

The above embodiments carrying the proviso that when R^7 is the formula:



then R^9 is other than hydrogen.

In a more preferred embodiment of the present invention, R^6 is selected from the following:

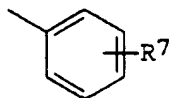


In the above, Y is selected from either a hydrogen atom or a chlorine atom.

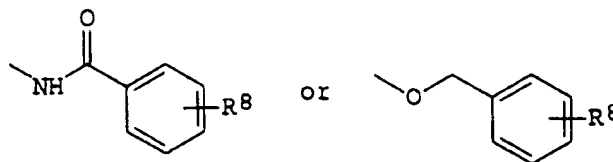
In a more preferred embodiment of the present invention, R^2 is selected from the following: a -COOH group or an ester or an amide thereof; a -CONHCH₂COOH group; a -CONHOCH₂Ph group; or a -CONHCH₂CONH₂ group.

In another preferred embodiment of the present invention, R^1 is a -CH₃ group, and R^2 is a -COOH group; a -CONHCH₂COOH group; a CONHOCH₂Ph group or a -CONHCH₂CONH₂ group, and R^3 and R^4 are hydrogen atoms. Also, X is -CO-, R^5 is -COOH, n is 1, and

R^6 is represented by the following formula

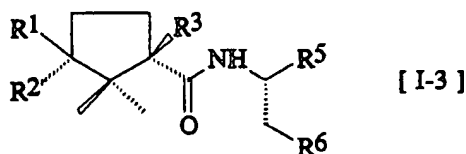


wherein R^7 is



and R^8 occurs 2 or 3 times and is a chlorine atom.

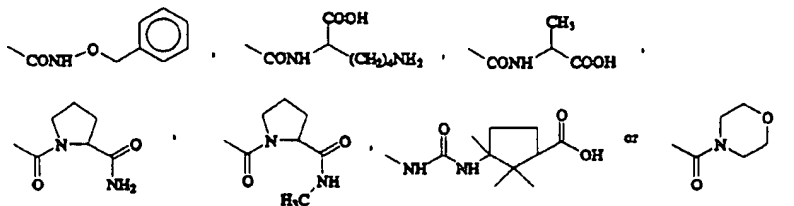
Other compounds within the scope of the present invention are compounds of the formula [I-3]:



[I-3]

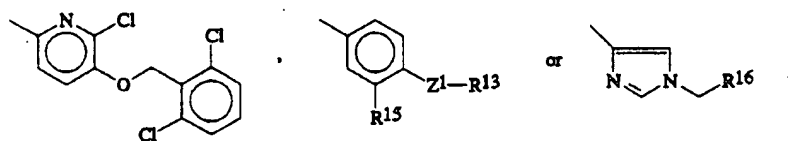
In the above formula [I-3], R^1 may be a hydrogen atom or a methyl group. Also in the above formula [I-3], R^2 may be selected from the following: a -CN group; a -COOH group; a -CONH₂ group; a -CONHOH group; a -CON(CH₃)₂ group; a -CH₂OCH₂COOH group; a -CH=CHCOOH group; a -CONHCH₂COOH group; a -CONH(CH₂)₂COOH group; a -

CONHCH₂CONH₂ group; a -CONH(CH₂)₂CN group; a group selected from the following:



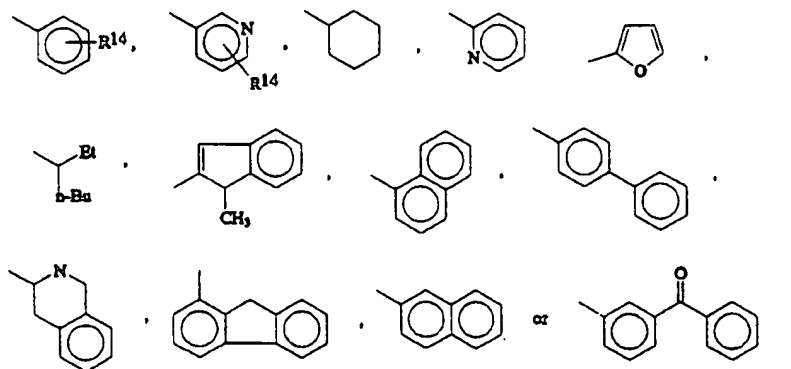
In the above formula [I-3], R³ may be a hydrogen atom or a methyl group and R⁵ may be a -COOH group or a COOMe group.

In the above formula [I-3], R^6 may be selected from the following:



In the above, Z¹ may be selected from the following:
a -O- group; a -NHCO- group; a -NHCH₂- group, a -OCH₂-
10 group; a -CONH-group; a -NHSO₂- group; a -NHCOCH₂- group;
or a -N(CH₃)CH₂- group.

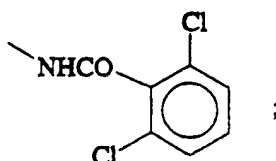
In the above, R¹³ may be selected from the following: a -H group; a -iBuO group; a -CH₃ group; a -i-Bu group; or a group selected from the following:



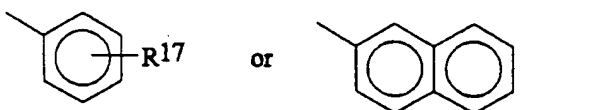
16

In the above, R^{14} , which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -F group; a -Cl group; a -Br group; an -I group; a -CH₃ group; a -OCH₃ group; a -CF₃ group; a -NO₂ group; a -NH₂ group; or a -n-C₇H₁₅ group.

In the above, R^{15} may be selected from the following: a -H group; a -OH group; a -NO₂ group; or a group selected from the following:

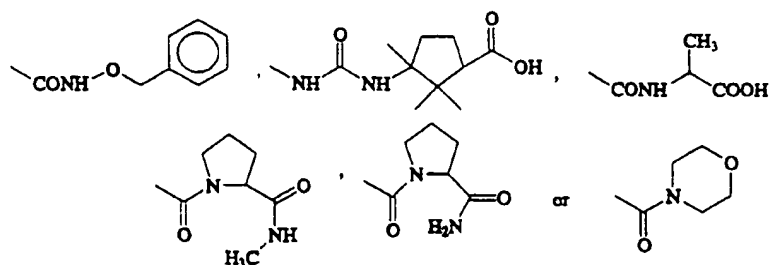


In the above, R^{16} may be selected from the following



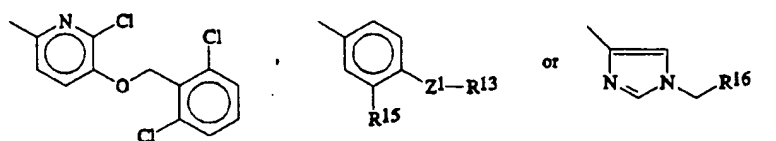
In the above, R^{17} , which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -Cl group; a -OCH₃ group; or a -CF₃ group, provided that R^1 and R^3 must be different.

In another embodiment of the compounds according to formula [I-3], R^1 is a hydrogen atom or a methyl group, and R^2 is selected from the following: a -CN group; a -COOH group; a -COOMe group; a -CONH₂ group; a -CONHOH group; a -CON(CH₃)₂ group; a -CH₂OCH₂COOH group; a -CH=CHCOOH group; a -CONHCH₂COOH group; a -CONH(CH₂)₂COOH group; a -CONHCH₂CONH₂ group; a -CONH(CH₂)₂CN group; or a group selected from the following:



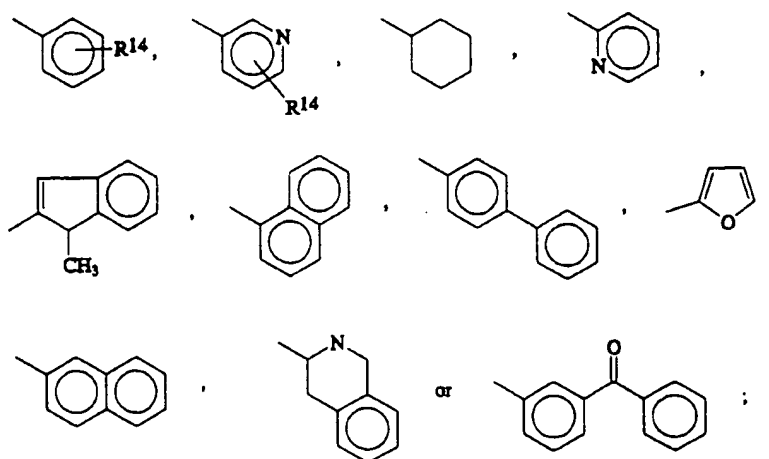
and R^3 is a hydrogen atom or a methyl group.

In the another embodiment of formula [I-3], R^5 is a -COOH group or a -COOMe group and R^6 is selected from the following:



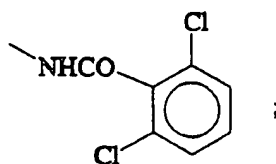
5 In the above embodiment of formula [I-3], Z^1 may be selected from the following: a -O- group; a -NHCO- group; a -NHCH₂- group; a -OCH₂- group; a -CONH- group; a -NHSO₂- group; or a -NHCOCH₂- group.

10 In the above embodiment of formula [I-3], R^{13} may be selected from the following: a -H group; a -iBuO group; a -i-Bu group; or a group selected from the following:

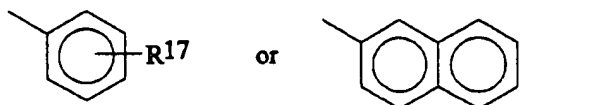


In the above embodiment of formula [I-3], R^{14} , which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -F group; a -Cl group; a -Br group; an -I group; a -CH₃ group; a -OCH₃ group; a -CF₃ group; a -NO₂ group; a -NH₂ group; or a -n-C₂H₅ group.

In the above embodiment of formula [I-3], R^{15} may be selected from the following: a -H group; a -OH group; a -NO₂ group; or a group selected from the following:

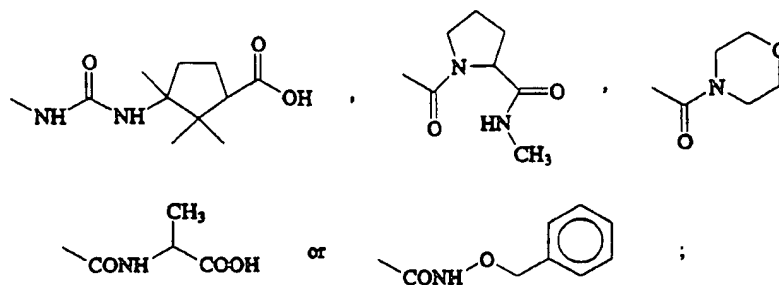


In the above embodiment of formula [I-3], R^{16} may be selected from the following:

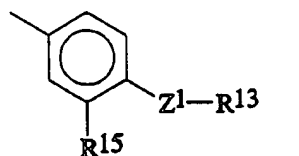


In the above embodiment of formula [I-3], R^{17} , which occurs one or more times and which may be the same or different in each occurrence, is a chlorine atom, provided that R^1 and R^3 must be different.

In another embodiment of formula [I-3], R^1 is methyl group and R^2 may be selected from the following: a -CN group; a -COOH group; a -CONH₂ group; a -CONHOH group; a -CH₂OCH₂COOH group; a -CH=CHCOOH group; a -CONHCH₂COOH group; a -CONH(CH₂)₂COOH group; a -CONHCH₂CONH₂ group; a -CONH(CH₂)₂CN group; or a group selected from the following:

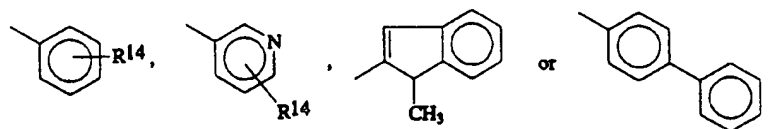


In the above, R_3 is a hydrogen atom, R^5 is a $-COOH$ group or a $-COOMe$ group and R^6 may be selected from the following:



In the above embodiment of formula [I-3], Z^1 may be selected from the following: a $-NHCO-$ group; a $-OCH_2-$ group; a $-NHCH_2-$ group; a $-CONH-$ group; or a $-NHSO_2-$ group.

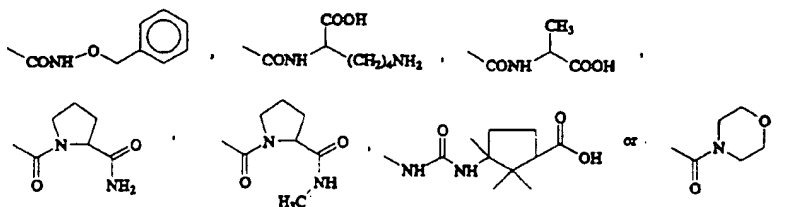
In the above embodiment of formula [I-3], R^{13} may be selected from the following:



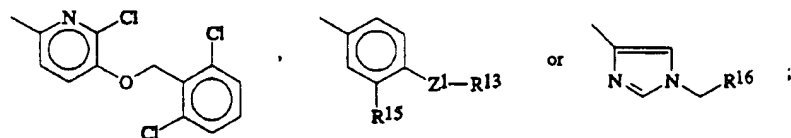
In another embodiment of formula [I-3], R^{14} , which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a $-F$ group; a $-Cl$ group; a $-Br$ group; an $-I$ group; a $-CH_3$ group; a $-OCH_3$ group; a $-CF_3$ group; or a $-NO_2$ group.

In another embodiment of formula [I-3], R^{15} may be a $-H$ group or a $-OH$ group.

In a another embodiment of formula [I-3], R^1 is a hydrogen atom or a methyl group and R^2 may be selected from the following: a -CN group; a -COOH group; a -CONH₂ group; a -CONHOH group; a -CONHOCH₃ group; a -CH₂OCH₂COOH group; a -CH=CHCOOH group; a -CONHCH₂COOH group; a -CONH(CH₂)₂COOH group; a -CONHCH₂CONH₂ group; a -CONH(CH₂)₂CN group; or a group selected from the following:



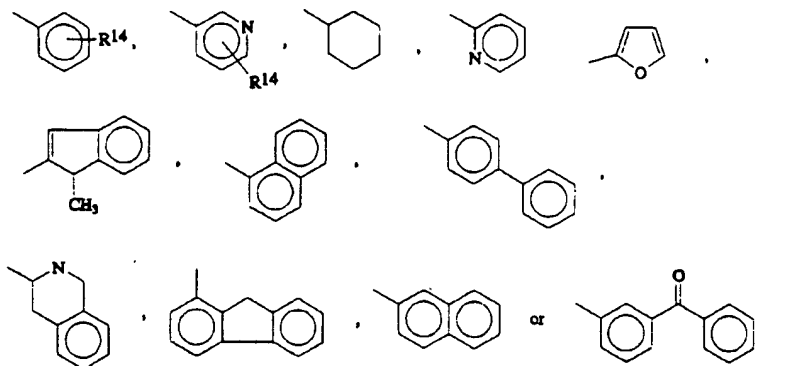
In another embodiment of formula [I-3], R^3 is a hydrogen atom or a methyl group, R^5 is a -COOH group or a -COOMe group, and R^6 may be selected from the following:



In another embodiment of formula [I-3], Z^1 may be selected from the following: a -O- group; a -NHCO- group; a -NHCH₂- group; a -OCH₂- group; a -CONH- group; or a -NHSO₂- group.

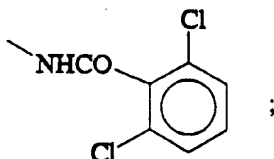
In another embodiment of formula [I-3], R^{13} may be selected from the following: a -H group; a -iBuO group; or a group selected from the following:

21

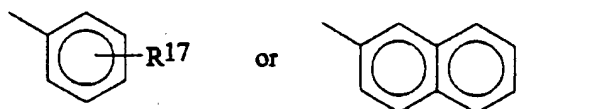


In another embodiment of formula [I-3], R¹⁴, which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -OH; a -F group; a -Cl group; a -Br group; an -I group; a -CH₃ group; a -OCH₃ group; a -CF₃ group; a -NO₂ group; or a -NH₂ group.

In another embodiment of formula [I-3], R¹⁵ may be selected from the following: a -H group; a -OH group; a -NO₂ group; or a group selected from the following:

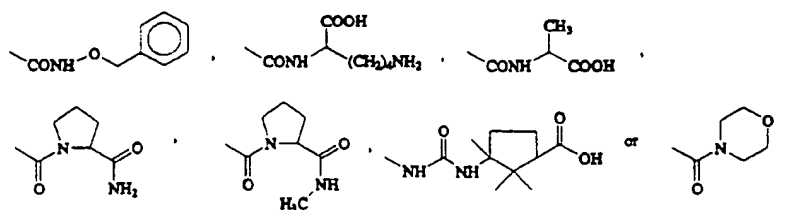


In another embodiment of formula [I-3], R¹⁶ may be selected from the following:



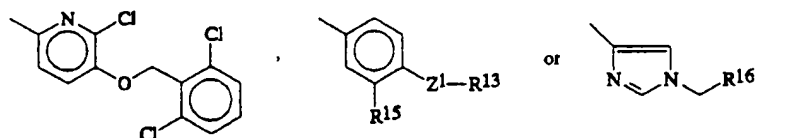
In another embodiment of formula [I-3], R¹⁷, which occurs one or more times and which may be the same or different in each occurrence, may be a -Cl group or a -CF₃ group, provided that R¹ and R³ must be different.

In another embodiment of formula [I-3], R^1 may be a hydrogen atom or methyl group, R^2 may be selected from the following: a -CN group; a -COOH group; a -CONH₂ group; a -CONHOH group; a -CH₂OCH₂COOH group; a
 5 -CH=CHCOOH group; a -CONHCH₂COOH group; a -CONH(CH₂)₂COOH group; a -CONHCH₂CONH₂ group; a -CONH(CH₂)₂CN group; or a group selected from the following:



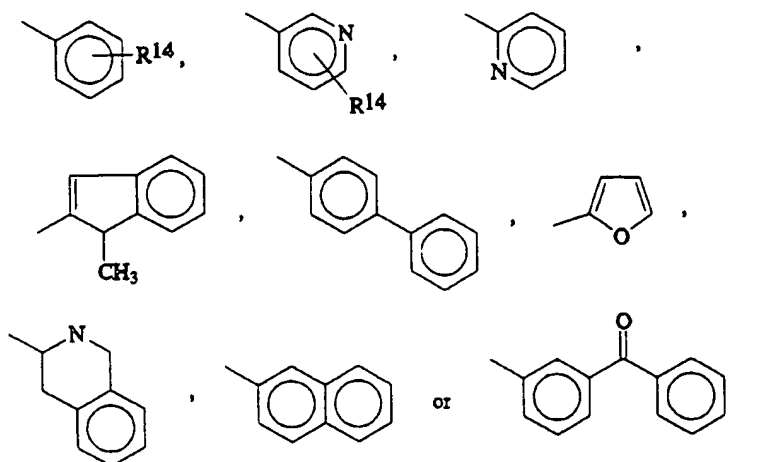
and R^3 may be a hydrogen atom or a methyl group.

In another embodiment of formula [I-3], R^5 is -COOH
 10 group or a -COOMe group and R^6 may be selected from the following:



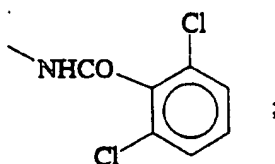
In another embodiment of formula [I-3], Z^1 may be selected from the following: a -O- group; a -NHCO- group; a -NHCH₂- group; a -OCH₂- group; a -CONH- group;
 15 or a -NHSO₂- group.

In another embodiment of formula [I-3], R^{13} may be a -H group or a group selected from the following:

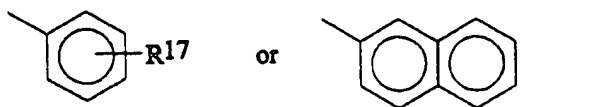


In another embodiment of formula [I-3], R¹⁴, which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -H group; a -F group; a -Cl group; a -Br group; an -I group; a -CH₃ group; a -OCH₃ group; a -CF₃ group; a -NO₂ group; or a -NH₂ group.

In another embodiment of formula [I-3], R¹⁵ may be selected from the following: a -H group; a -OH group, a -NO₂ group; or a group selected from the following:



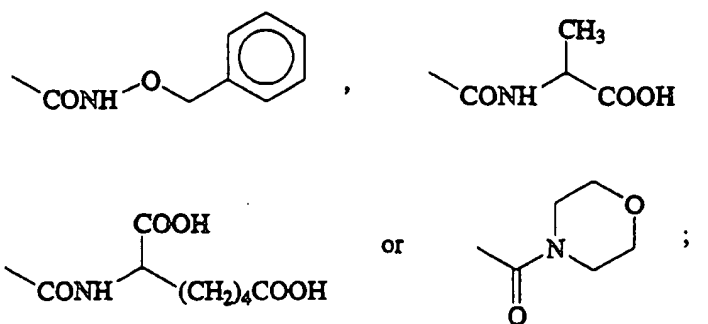
In another embodiment of formula [I-3], R¹⁶ may be selected from the following:



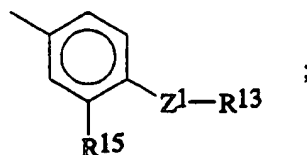
In another embodiment of formula [I-3], R¹⁷, which occurs one or more times and which may be the same or

different in each occurrence, may be a -H group or a -Cl group, provided that R^1 and R^3 must be different.

In another embodiment of formula [I-3], R^1 is a methyl group, and R^2 may be selected from the following:
 5 a -CN group; a -COOH group; a -CONH₂ group; a -CONHOH group; a -CH₂OCH₂COOH group; a -CH=CHCOOH group; a -CONHCH₂COOH group; a -CONH(CH₂)₂COOH group; a -CONH(CH₂)₂CN group; a -CONHCH₂CONH₂ group; or a group selected from the following:

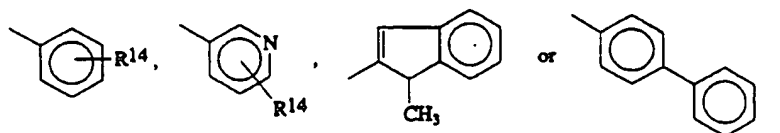


10 In another embodiment of formula [I-3], R^3 is a hydrogen atom, R^5 is a -COOH group or a -COOMe group, and R^6 may be selected from the following:



In another embodiment of formula [I-3], Z^1 may be selected from the following: a -NHCO- group; a -NHCH₂- group; a -NACCH₂- group; a -OCH₂- group; or a -CONH- group.
 15

In another embodiment of formula [I-3], R^{13} may be selected from the following:



In another embodiment of formula [I-3], R¹⁴, which occurs one or more times and which may be the same or different in each occurrence, may be selected from the following: a -F group; a -Cl group; a -Br group; an -I group; a -OCH₃ group; a -CF₃ group; or a -NO₂ group.

In another embodiment of formula [I-3], R¹⁵ is a -H group or a -NO₂ group.

Preferred compounds according to formula [I] may be selected from the group consisting of (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)-carbonyl]-1-[(3,4-dichlorophenyl)methyl]-L-histidine, (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine, (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine, (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-3-nitro-L-tyrosine, (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2,4,6-trichlorophenyl)carbonyl]-amino]-L-phenylalanine, (1S-cis)-N-[[3-[(2-Amino-2-oxoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine, (1S-cis)-N-[[3-[(Carboxymethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine, and (1S-cis)-N-[(3-Cyano-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine.

The desired compounds of the present invention may exist in the form of optical isomers based on asymmetric carbon atoms thereof, and the present invention also includes these optical isomers and mixtures thereof.

In an embodiment of the present invention, the steric configuration of a bond need not be fixed. A bond may be of any acceptable configuration. Further,

a compound may be a mixture with several different configurations of the same bond.

The desired compounds of the present invention may be used in the form of an ester or amide thereof. As
5 the ester thereof, there may be mentioned a C₁₋₆ alkyl ester, a C₂₋₇ alkenyl ester, a C₂₋₇ alkynyl ester, a C₂₋₇ alkanoyloxy-C₁₋₆ alkyl ester, an aryl-C₁₋₆ alkyl ester or an aryl ester. As the amide thereof, there may be
10 mentioned an amide (-CONH₂), a mono or di N-C₁₋₆ alkyl amide, an N-C₃₋₈ cycloalkyl amide, an N-aryl amide or an N-aryl-C₁₋₆ alkyl amide.

The desired compound of the present invention may be clinically used either in a free form or in the form of pharmaceutically acceptable salts thereof.
15 Pharmaceutically acceptable salts include acid-addition salts with inorganic acid or organic acid (e.g., hydrochloride, sulfate, nitrate, hydrobromide, methanesulfonate, p-toluenesulfonate, acetate), salt
20 with inorganic base, organic base or amino acid (e.g., triethylamine salt, a salt with lysine, an alkali metal salt, an alkali earth metal salt and the like).

The compound may also be formulated into a pharmaceutical composition comprising a therapeutically effective amount of the compound as defined above and a
25 pharmaceutically acceptable carrier or diluent.

The compound can also be used for treating or preventing $\alpha_4\beta_1$ adhesion mediated conditions in a mammal such as a human. This method may comprise administering to a mammal or a human patient an effective amount of
30 the compound or composition as explained above.

This method can be used to treat such inflammatory conditions as rheumatoid arthritis, asthma, allergy conditions, adult respiratory distress syndrome, AIDS, cardiovascular diseases, thrombosis or harmful platelet
35 aggregation, reocclusion following thrombolysis, allograft rejection, reperfusion injury, psoriasis, eczema, contact dermatitis and other skin inflammatory

diseases, osteoporosis, osteoarthritis, atherosclerosis, neoplastic diseases including metastasis of neoplastic or cancerous growth, wound healing enhancement, treatment of certain eye diseases such as detaching retina, Type I diabetes, multiple sclerosis, systemic lupus erythematosus (SLE), inflammatory and immunoinflammatory conditions including ophthalmic inflammatory conditions and inflammatory bowel diseases, ulcerative colitis, atherosclerosis, regional enteritis and other autoimmune diseases.

The desired compound of the present invention or pharmaceutically acceptable salts thereof may be administered either orally or parenterally, and it may be used as a suitable pharmaceutical preparation, for example, a tablet, a granule, a capsule, a powder, an injection, and an inhalation by a conventional process.

The dose of the desired compound of the present invention or a pharmaceutically acceptable salt thereof varies depending on an administration method, age, body weight, and state of a patient, but, in general, the daily dose is preferably about 0.1 to 100 mg/kg/day, particularly preferably 1 to 100 mg/kg/day.

Preferred routes of administration for asthma:

It is preferred that the compound of the present invention be administered in the form of an Aerosol. However, other routes of administration include intravenous, oral, intramuscular, and subcutaneous.

In the case of aerosol administration, compositions containing the compounds of the present invention can be prepared to provide for an excellent means for administering in aerosol form for inhalation therapy. Accordingly, the present invention will provide for self-propelling compositions containing the compounds of the present invention.

Propellants employed should be non-toxic and have a vapor pressure suitable for the conditions under which administration occurs. These propellants can be fluorinated or fluorochlorinated lower saturated aliphatic hydrocarbons. The preferred propellants of this type are the halogenated alkanes containing not more than two carbon atoms and at least one fluorine atom. Illustrative of these are trichloromonofluoromethane, dichlorodifluoromethane, monochlorotrifluoromethane, dichloromonofluoromethane and 1,2-dichloro-1,1,2,2-tetrafluoroethane. These compounds are available from E.I. duPont de Nemours and Company under the trade name "Freon". These propellants may be employed singularly or in admixture.

In addition to the propellant, an organic solvent may also be employed. The organic solvent must be non-toxic and without undesirable effects on inhalation in the amount present in the aerosol produced. In addition, the solvent should be substantially anhydrous, completely miscible with the propellant or mixture of propellants employed and have a suitable boiling point. Examples of such solvents included non-toxic aliphatic alcohols such as ethanol; ethers such as ethyl ether and vinyl ether; ketones such as acetone; and suitable halogenated lower alkanes.

In addition to the organic solvent, the composition may also optionally contain a non-toxic hygroscopic glycol. The glycol must be substantially miscible with the organic solvent and the propellant employed. Satisfactory glycols include propylene glycol, triethylene glycol, glycerol, butylene glycol and hexylene glycol.

The above indicated methods of administration and formulation of aerosol compositions should not be viewed as limiting. The compounds of the present invention can be formulated in anyway deemed suitable to one of

ordinary skill in the art so as to obtain the desired effects.

Pharmaceutical Compositions

As indicated previously, the compounds of formula (I) can be formulated into pharmaceutical compositions. In determining when a compound of formula (I) is indicated for the treatment of a given disease, the particular disease in question, its severity, as well as the age, sex, weight, and condition of the subject to be treated, must be taken into consideration and this perusal is to be determined by the skill of the attendant physician.

For medical use, the amount of a compound of Formula (I) required to achieve a therapeutic effect will, of course, vary both with the particular compound, the route of administration, the patient under treatment, and the particular disorder or disease being treated. A suitable daily dose of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for a mammalian subject suffering from, or likely to suffer from, any condition as described hereinbefore is 0.1 mg to 100 mg of the compound of formula I, per kilogram body weight of the mammalian subject. In the case of systematic administration, the dose may be in the range of 0.5 to 500 mg of the compound per kilogram body weight, the most preferred dosage being 0.5 to 50 mg/kg of mammal body weight administered two to three times daily. In the case of topical administration, e.g., to the skin or eye, a suitable dose may be in the range of 0.1 μ g to 100 μ g of the compound per kilogram, typically about 0.1 μ g/kg.

In the case of oral dosing, a suitable dose of a compound of Formula (I), or a physiologically acceptable salt thereof, may be as specified in the preceding paragraph, but most preferably is from 1 mg to 10 mg of the compound per kilogram, the most preferred dosage

being from 1 mg to 5 mg/kg of mammal body weight, for example, from 1 to 2 mg/kg. Most preferably, a unit dosage of an orally administrable composition encompassed by the present invention contains less than
5 about 1.0 g of a formula (I) compound.

It is understood that formulation, both for human and veterinary use, of the present invention may be presented to the mammal by inhalation. To achieve therapeutic effect, the dose may be in the range of 0.5
10 to 500 mg of the compound, per kg body weight. The most preferred dosage being 0.5 to 50 mg/kg of mammal body weight administered two to three times daily.

It is understood that the ordinarily skilled physician or veterinarian will readily determine and
15 prescribe the effective amount of a compound of Formula I to prevent or arrest the progress of the condition for which treatment is administered. In so proceeding, the physician or veterinarian could employ relatively low doses at first, subsequently increasing the dose until
20 a maximum response is obtained.

The compounds and compositions of the present invention can be administered to patients suffering from a condition listed herein in an amount which is effective to fully or partially alleviate undesired
25 symptoms of the condition. The symptoms may be caused by inappropriate cell adhesion mediated by $\alpha_4\beta_1$ integrins. Such inappropriate cell adhesion would typically be expected to occur as a result of increased VCAM-1 and/or CS-1 expression on the surface of
30 endothelial cells. Increased VCAM-1 and/or CS-1 expression can be due to a normal inflammation response or due to abnormal inflammatory states. In either case, an effective dose of a compound of the invention may reduce the increased cell adhesion due to increased
35 VCAM-1 expression by endothelial cells. Reducing the adhesion observed in the disease state by 50% can be considered an effective reduction in adhesion. More

preferably, a reduction in adhesion by 90%, is achieved. Most preferably adhesion mediated by VCAM-1/ $\alpha_4\beta_1$ and/or CS-1 interaction is abolished by an effective dose. Clinically, in some instances, effect of the compound
5 can be observed or a decrease in white cell infiltration into tissues or a site of injury. To achieve a therapeutic effect, then, the compounds or compositions of the present invention are administered to provide a dose effective to reduce or eliminate inappropriate cell
10 adhesion or to alleviate undesired symptoms.

While it is possible for an active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation comprising a compound of Formula (I) and a pharmaceutically acceptable carrier
15 thereof. Such formulations constitute a further feature of the present invention.

The formulations, both for human and veterinary medical use, of the present invention comprise an active ingredient of Formula (I), in association with a
20 pharmaceutically acceptable carrier thereof and optionally other therapeutic ingredient(s), which are generally known to be effective in treating the disease or condition encountered. The carrier(s) must be "acceptable" in the sense of being compatible with the
25 other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular, and
30 intravenous), intra-articular, topical, nasal inhalation (e.g., with an aerosol) or buccal administration. Such formulation are understood to include long-acting formulations known in the art.

The formulations may conveniently be presented in
35 unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods may include the step of bringing the active ingredient

into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired form.

Formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient in the form of a powder or granules; in the form of a solution or suspension in an aqueous liquid. Formulations for other uses could involve a nonaqueous liquid; in the form of an oil-in-water emulsion or a water-in-oil emulsion; in the form of an aerosol; or in the form of a cream or ointment or impregnated into a transdermal patch for use in administering the active ingredient transdermally, to a patient in need thereof. The active ingredient of the present inventive compositions may also be administered to a patient in need thereof in the form of a bolus, electuary, or paste.

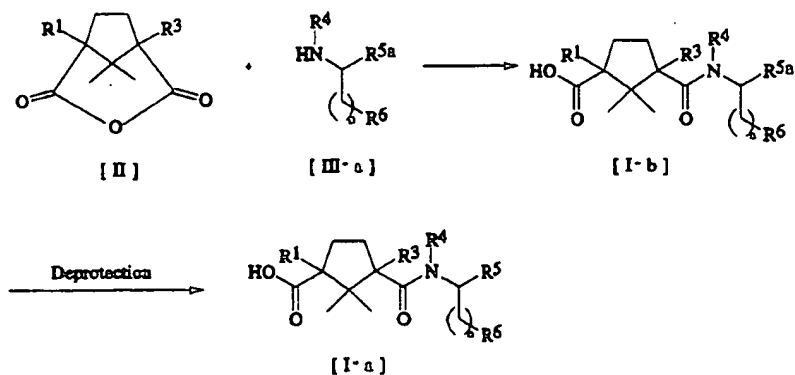
The practitioner is referred to "Remington: The Science and Practice of Pharmacy," 19th Edition, c. 1995 by the Philadelphia College of Pharmacy and Science, as a comprehensive tome on pharmaceutical preparations.

Abbreviations

Ac ₂ O:	Acetic anhydride
30 AcOEt:	Ethyl acetate
BCECF-AM:	2',7'-bis-(2-carboxyethyl)-5-(and 6-) carboxyfluorescein acetoxymethyl ester
BOP-Cl:	Bis (2-oxo-3-oxazolidinyl) phosphinic chloride

	BOP Reagent:	Benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorophosphate
	DMEM:	Dulbecco's Minimal Eagle's Media
5	DMF:	Dimethyl formamide
	DIEA:	Diisopropylethylamine
	EDC:	1-(3-Dimethylaminopropyl)-3- ethylcarbodiimide hydrochloride
	Et:	Ethyl
10	EtOH:	Ethanol
	HATU:	N-[(Dimethylamino)-1H-1,2,3-triazolo[4,5- b]-pyridin-1-ylmethylene]-N- methylmethanaminium hexafluorophosphate N-oxide
15	HBSS:	Hank's Balanced Salt Solution
	HBTU:	O-Benzotriazol-1-yl-N,N,N',N'- tetramethyluronium hexafluorophosphate
	HOBt:	1-Hydroxybenzotriazole
	HSA:	Human serum albumin
20	LDA:	Lithium diisopropylamide
	Me:	Methyl
	meq:	milliequivalent
	MeOH:	Methanol
	n-Bu:	n-Butyl
25	NMP:	1-Methyl-2-pyrrolidinone
	PBS:	Phosphate buffered saline
	Pd-C:	Palladium on charcoal
	Ph:	Phenyl
	SPDP:	3-(2-pyridyldithio)propionic acid N- hydroxysuccinimide ester
30	t-Bu:	t-butyl
	THF:	Tetrahydrofuran
	TFA:	Trifluoroacetic acid

According to the present invention, the desired compound
35 [I] can be prepared by the following methods:

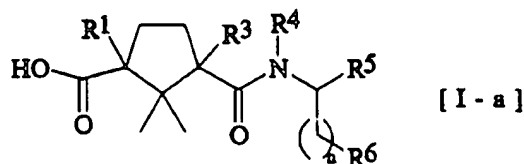
Scheme 1 (Method A):

wherein R^{5a} is a group of the formula: -COOR²²,
 -(C₁₋₆ alkylene)COOR²², -(C₁₋₇ alkylene)O(C₁₋₆ alkyl),
 -(C₁₋₇alkylene)OH, -COO(C₁₋₆ alkyl), -CONH(C₁₋₆ alkyl) or
 5 -CONH₂,

R²² is a protecting group for the carboxyl group,
 and the other symbols are the same as defined above.

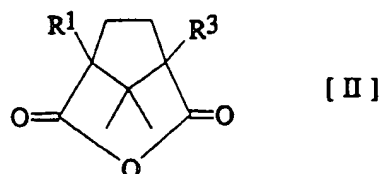
Method A:

The compound of the formula [I] wherein R² is a
 10 group of the formula: -COOH and X is a group of the
 formula: -CO-, an ester thereof, an amide thereof or a
 pharmaceutically acceptable salt thereof, i.e., the
 compound of the formula [I-a]:

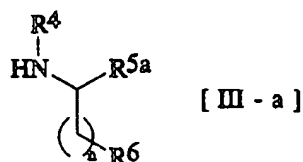


wherein the symbols are the same as defined above, an
 15 ester thereof, an amide thereof or a pharmaceutically
 acceptable salt thereof may be prepared by
 (1) reacting a compound of the formula [II]:

35



wherein the symbols are the same as defined above,
with a compound of the formula [III-a]:



wherein the symbols are the same as defined above,
or a salt thereof,

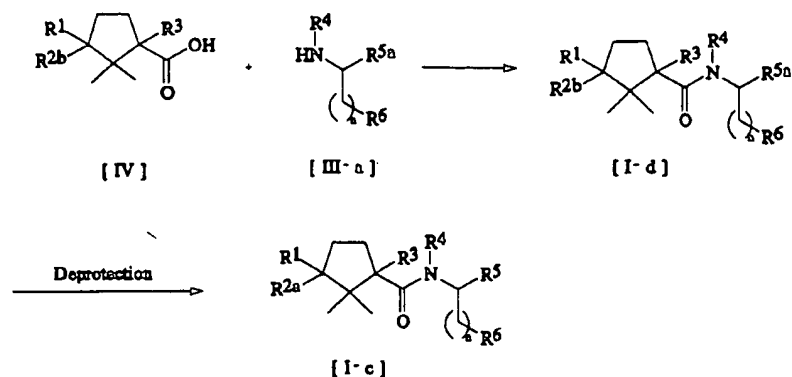
- 5 (2) removing the protecting group for the carboxyl group, if desired, and
- (3) converting the resulting compound into an ester thereof, an amide thereof or a pharmaceutically acceptable salt thereof by a conventional method, if
- 10 further desired.

R²² can be selected from a conventional protecting group for a carboxyl group, for example, a C₁₋₆ alkyl group, a C₂₋₇ alkenyl group, a C₂₋₇ alkynyl group, a C₂₋₇ alkanoyloxy-C₁₋₆ alkyl group, an aryl-C₁₋₆ alkyl group (e.g., benzyl group) or an aryl group (e.g., phenyl group) and the like.

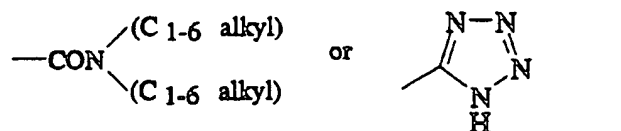
A salt of the compound [III-a] includes, for example, salt with an inorganic acid (e.g., hydrochloride, sulfate) and salt with an inorganic base (e.g., an alkali metal salt such as sodium salt or potassium salt,

an alkali earth metal salt such as magnesium salt or calcium salt).

- The reaction of the compound [II] and the compound [III-a] or a salt thereof is carried out in the presence of a base in a suitable solvent or without a solvent. The base can be selected from an organic base (e.g., DIEA, DMAP, Et₃N, DBU), an alkali metal hydride (e.g., NaH, LiH), an alkali metal carbonate (e.g., Na₂CO₃, Na₂KO₃), an alkali metal hydrogen carbonate (e.g., NaHCO₃, KHCO₃), an alkali metal amide (e.g., NaNH₂), an alkali metal alkoxide (e.g., NaOMe, KOMe), an alkyl-alkali metal (n-BuLi, t-BuLi), an alkali metal hydroxide (e.g., NaOH, KOH), an alkali earth metal hydroxide (e.g., Ba(OH)₂), and the like. The solvent can be selected from any one which does not disturb the reaction, for example, DMF, THF, benzene, toluene, DMSO, CH₃CN or a mixture thereof. The reaction is preferably carried out at a temperature from 0°C to 100°C, more preferably at a temperature from 40°C to 80°C.
- The removal of said protecting group from the products can be carried out by a conventional method, which is selected according to the types of the protecting groups to be removed, for example, hydrolysis, acid treatment, catalytic reduction, and the like.
- A more preferred method than method A is:
Scheme 2 (Method B):

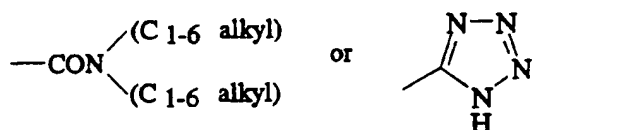


- R^{2a} is a group of the formula: -CN, -COOR²³, -COOH, - (C₁₋₆ alkylene)OH, -CH₂O(C₁₋₆ alkyl), - (C₁₋₆ alkylene)COOH, - (C₁₋₆ alkylene)COOR²³, -CH₂O(C₁₋₆ alkylene)O(C₁₋₆ alkyl), -CH₂O(C₁₋₆ alkylene)COOH, -CH₂O(C₁₋₆ alkylene)COOR²³,
- 5 - (C_{2,7} alkenylene)COOH, - (C_{2,7} alkenylene)COOR²³, -CO(C₁₋₆ alkylene)COOH, -CO(C₁₋₆ alkylene)COOR²³, -CO(C_{2,7} alkenylene)COOH, -CO(C_{2,7} alkenylene)COOR²³, -CO(C₁₋₆ alkylene)O(C₁₋₆ alkyl), -CO(C₁₋₆ alkylene)CO(C₁₋₆ alkyl),
- 10 -CONH(C₁₋₆ alkyl), -CONHO(C₁₋₆ alkyl), -CONH(C₁₋₆ alkylene)COOH, -CONH(C₁₋₆ alkylene)COOR²³, -CONH(C_{3,7} cycloalkyl), -CONH₂, -CONH(C₁₋₆ alkylene)CONH₂, -CONHOH, -NHCO₂CH₂Ph, -CONHOCH₂Ph, -CONH(C₁₋₆alkylene)CN, -COO(C₁₋₆alkyl), -CH₂O(C₁₋₆alkylene)CONH₂,



- 15 R^{2b} is a group of the formula: -CN, -COOR²³, - (C₁₋₆ alkylene)OH, -CH₂O(C₁₋₆ alkyl), - (C₁₋₆ alkylene)COOR²³, -CH₂O(C₁₋₆ alkylene)O(C₁₋₆ alkyl), -CH₂O(C₁₋₆ alkylene)COOR²³, - (C_{2,7} alkenylene)COOR²³, -CO(C₁₋₆ alkylene)COOR²³, -CO(C_{2,7} alkenylene)COOR²³,
- 20 -CO(C₁₋₆ alkylene)O(C₁₋₆ alkyl), -CO(C₁₋₆ alkylene)CO(C₁₋₆ alkyl),

- CONH(C₁₋₆ alkyl), -CONHO(C₁₋₆ alkyl),
 -CONH(C₁₋₆ alkylene)COOR²³, -CONH(C₃₋₇ cycloalkyl), -CONH₂,
 -CONH(C₁₋₆ alkylene)CONH₂, -CONHOH, -NHCO₂CH₂Ph,
 -CONHOCH₂Ph, -CONH(C₁₋₆alkylene)CN, -COO(C₁₋₆alkyl),
 5 -CH₂O(C₁₋₆alkylene)CONH₂,

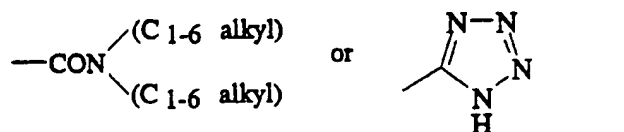


R²³ is a protecting group for the carboxyl group, and the other symbols are the same as defined above.

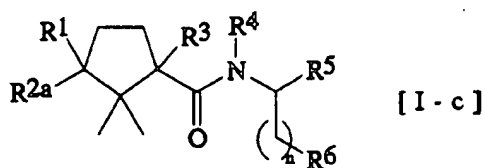
Method B:

- The compound of the formula [I], an ester thereof,
 10 an amide thereof or a pharmaceutically acceptable salt thereof,

- wherein R² is a group of the formula: -CN, -COOR²³, -COOH,
 -(C₁₋₆ alkylene)OH, -CH₂O(C₁₋₆ alkyl), -(C₁₋₆ alkylene)COOH,
 -(C₁₋₆ alkylene)COOR²³, -CH₂O(C₁₋₆ alkylene)O(C₁₋₆ alkyl),
 15 -CH₂O(C₁₋₆ alkylene)COOH, -CH₂O(C₁₋₆ alkylene)COOR²³,
 -(C₂₋₇ alkenylene)COOH, -(C₂₋₇ alkenylene)COOR²³,
 -CO(C₁₋₆ alkylene)COOH, -CO(C₁₋₆ alkylene)COOR²³,
 -CO(C₂₋₇ alkenylene)COOH, -CO(C₂₋₇ alkenylene)COOR²³,
 -CO(C₁₋₆ alkylene)O(C₁₋₆ alkyl),
 20 -CO(C₁₋₆ alkylene)CO(C₁₋₆ alkyl),
 -CONH(C₁₋₆ alkyl), -CONHO(C₁₋₆ alkyl),
 -CONH(C₁₋₆ alkylene)COOH, -CONH(C₁₋₆ alkylene)COOR²³,
 -CONH(C₃₋₇ cycloalkyl), -CONH₂, -CONH(C₁₋₆ alkylene)CONH₂,
 -CONHOH, -NHCO₂CH₂Ph, CONHOCH₂Ph, -CONH(C₁₋₆alkylene)CN,
 25 -COO(C₁₋₆alkyl), -CH₂O(C₁₋₆alkylene)CONH₂ or



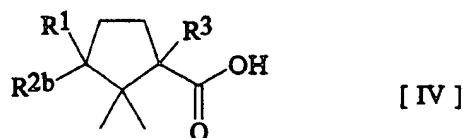
X is a group of the formula: -CO-, i.e., the compound of the formula [I-c]:



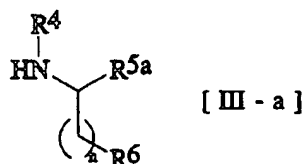
wherein

the symbols are the same as defined above, may be prepared by

(1) condensing a compound of the formula [IV]:



5 wherein the symbols are the same as defined above, or a salt thereof, with a compound of the formula [III-a]:



 wherein the symbols are the same as defined above, or a salt thereof,

10 (2) removing the protecting group for the carboxyl group and hydroxyl group, if desired, and

 (3) converting the resulting compound into an ester thereof, an amide thereof or a pharmaceutically acceptable salt thereof by a conventional method, if
15 further desired.

R^{22} and R^{23} are the same or different conventional protecting group for a carboxyl group, for example, a C_{1-6}

alkyl group, a C₂₋₇ alkenyl group, a C₂₋₇ alkynyl group, a C₂₋₇ alkanoyloxy-C₁₋₆ alkyl group, an aryl-C₁₋₆ alkyl group (e.g., benzyl group) or an aryl group (e.g., phenyl group) and the like.

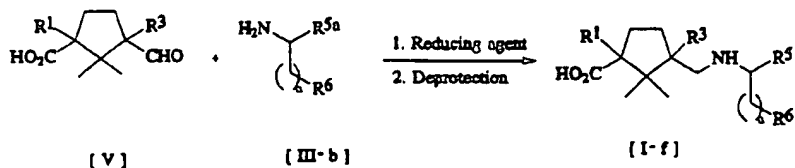
- 5 A salt of the compound [III-a] and/or [IV] includes, for example, salt with an inorganic acid (e.g., hydrochloride, sulfate) and salt with an inorganic base (e.g., an alkali metal salt such as sodium, potassium and calcium, an alkali earth metal salt such as
10 barium).

The condensation reaction of the compound [IV] or a salt thereof with the compound [III-a] or a salt thereof is carried out in the presence of a condensing reagent in a suitable solvent or without a solvent. The condensing
15 reagent can be selected from any one which can be used for a conventional peptide synthesis, for example, BOP-Cl, BOP reagent, DCC and WSCI.

The solvent can be selected from any one which does not disturb the condensation reaction, for example, CH₂Cl₂,
20 DMF or a mixture thereof. The reaction is preferably carried out at a room temperature.

The removal of said protecting group from the products can be carried out by a conventional method, which is selected according to the types of the protecting groups
25 to be removed, for example, hydrolysis, acid treatment, catalytic reduction, and the like.

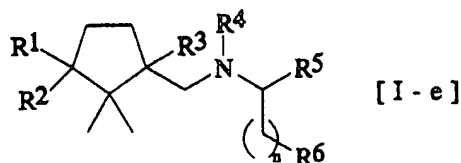
Scheme 3 (Method C):



wherein the symbols are the same as defined above.

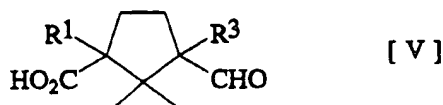
Method C:

The compound of the formula [I] wherein X is a methylene group, an ester thereof, an amide thereof or a pharmaceutically acceptable salt thereof, i.e., the compound of the formula [I-e]:

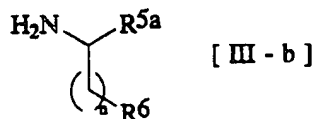


wherein

the symbols are the same as defined above, an ester thereof, an amide thereof or a pharmaceutically acceptable salt thereof, may be prepared by
 (1) reacting a compound of the formula [V]:



wherein the symbols are the same as defined above, or a salt thereof in the presence of a reducing agent with a compound of the formula [III-b]:



wherein the symbols are the same as defined above,
 (2) removing the protecting group for the carboxyl group, if desired, and

(3) converting the resulting compound into an ester thereof, an amide thereof or a pharmaceutically acceptable salt thereof by a conventional method, if further desired.

- 5 A salt of the compound [V] and/or [III-b] includes, for example, salt with an inorganic acid (e.g., hydrochloride, sulfate) and salt with an inorganic base (e.g., an alkali metal salt, an alkali earth metal salt).
- 10 The reductive alkylation of the compound [V] or a salt thereof with the compound [III-b] or a salt thereof is carried out by a conventional method in the presence of a reducing agent in a suitable solvent or without a solvent. The reducing agent is preferably sodium
- 15 borohydride, sodium cyanoborohydride, and the like. The solvent can be selected from any one which does not disturb the reaction, for example, alkanol such as methanol, alkanolic acid such as AcOH, THF or a mixture thereof. The reaction is preferably carried out at a
- 20 temperature from 0°C to a room temperature.

The reaction of the compound [I-f] or a salt thereof and the compound [VII] is carried out in the presence of an acid acceptor in a suitable solvent or without a solvent. The acid acceptor and the solvent can be

25 selected from the base or the solvent used in Method A. The reaction is preferably carried out at room temperature.

The removal of said protecting group from the products can be carried out by a conventional method, which is

30 selected according to the types of the protecting groups to be removed, for example, hydrolysis, acid treatment, catalytic reduction, and the like.

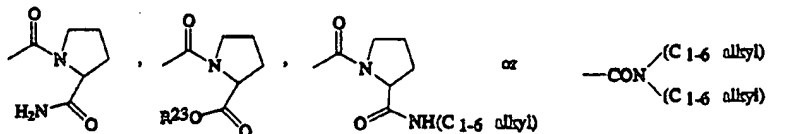
The desired compound [I] of the present invention can be converted to each other. Such conversion of the present compound [I] into the other compound [I] may be carried out by selecting one of the following procedures from (a) to (e) according to the type of substituent thereof, and if desired, followed by removing the protecting group for the carboxyl group by a conventional method.

Procedure (a):

The compound [I] wherein R⁶ is an amino-substituted aryl group can be prepared by the reduction of the compound [I] wherein the corresponding R⁶ is an aralkyloxycarbonyl amino group- or nitro- substituted aryl group. The reduction can be, for example, a catalytic reduction using a palladium catalyst such as palladium on an activated carbon, a platinum catalyst such as platinum oxide, and the like. The catalytic reduction is preferably carried out at a room temperature.

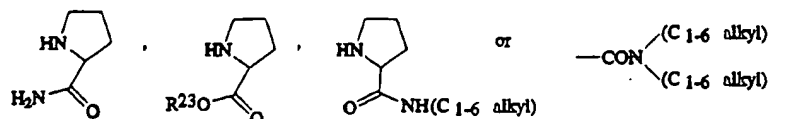
Procedure (b):

The compound [I] wherein R² is a group of the formula: -CONH₂, -CONH(C₁₋₆ alkyl), -CONHO(C₁₋₆ alkyl), -CONH(C₁₋₆ alkylene)COOR²³, -CONH(C_{3,7} cycloalkyl), -CONH(C₁₋₆ alkylene)CONH₂, -CONHOCH₂Ph, -CONH(C₁₋₆ alkylene)CN, CONHOH,



can be prepared by reacting the compound [I] wherein the corresponding R² is a group of the formula: -COOH with a substituted or unsubstituted amine selected from a group of the formula: NH₃, NH₂(C₁₋₆ alkyl), NH₂O(C₁₋₆ alkyl), NH₂(C₁₋₆ alkylene)COOR²³, NH₂(C_{3,7} cycloalkyl),

$\text{NH}_2(\text{C}_{1-6} \text{ alkylene})\text{CONH}_2$, NH_2OH , $\text{NH}_2\text{OCH}_2\text{Ph}$, $\text{NH}_2(\text{C}_{1-6} \text{ alkylene})\text{CN}$,



wherein R^{23} is defined as above, in the presence of a condensing reagent (e.g., BOP reagent) which can be used for a conventional peptide synthesis, and removing the protecting group for the carboxyl group, if desired.

5 The reaction is preferably carried out at a temperature from 0°C to a room temperature.

Procedure (c):

10 The compound [I] wherein R^4 is a C_{1-6} alkyl group can be prepared by reacting the compound [I] wherein the corresponding R^4 is a hydrogen atom with a C_{1-6} alkyl halide (e.g., methyl iodide, butyl iodide) in the presence of metal hydride (e.g., NaH). The reaction is

15 preferably carried out at a temperature from 0°C to room temperature.

Procedure (d):

The compound [I] wherein R^6 is a C_{2-6} alkanoylamino-, C_{3-7} cycloalkylcarbonylamino-,

20 aryl C_{2-7} alkanoylamino-, arylcarbonylamino-, C_{1-5} alkyloxycarbonylamino-, C_{3-7} cycloalkyloxycarbonylamino-, aryl C_{1-6} alkyloxycarbonylamino-, arylureido, or arylsulfonylamino-substituted aryl group can be prepared by reacting the compound [I] wherein the corresponding

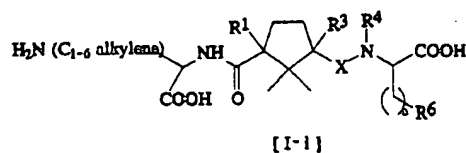
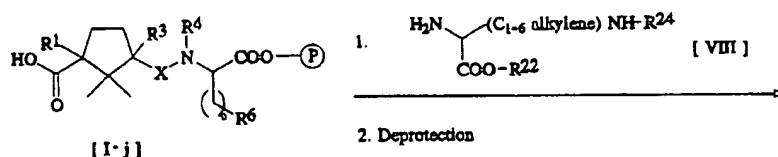
25 R^6 is an amino aryl group or a $(\text{C}_{1-6} \text{ alkyl})$ -amino-substituted aryl group with a C_{2-6} alkanolic acid, an anhydride of C_{2-6} alkanolic acid, C_{2-6} alkanoyl halide, C_{3-7} cycloalkanecarboxylic acid, anhydride of C_{3-7} cycloalkanecarboxylic acid, C_{3-7} cycloalkanoyl halide, aryl C_{2-7}

30 alkanolic acid, anhydride of aryl C_{2-7} alkanolic acid, aryl

- 5 C₂₋₇ alkanoyl halide, arylcarboxylic acid, anhydride of arylcarboxylic acid, arylcarbonyl halide, C₁₋₃ alkyl halogenoformate, arylisocyanate, or arylsulfonyl halide in the presence or absence of an acid acceptor (e.g., DIEA) and in the presence or absence of a condensing reagent (e.g., BOP-Cl) which can be used for a conventional peptide synthesis. The reaction is preferably carried out at a temperature from 0°C to a room temperature.

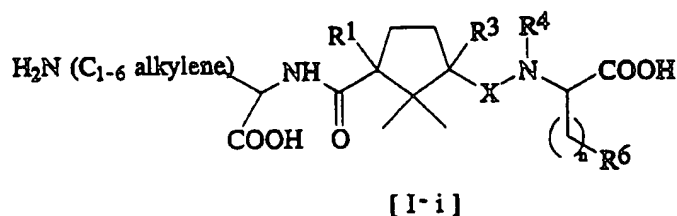
10 Procedure (e):

(P) = a resin which is used in a conventional solid phase peptide synthesis

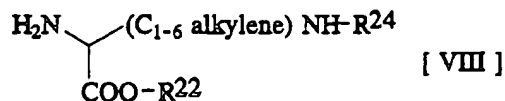


wherein R²⁴ is a protecting group for the amino group, and the other symbols are the same as defined above.

The compound of the formula [I-i]:



can be prepared by condensing the compound [I] wherein the corresponding R^2 is a group of the formula: $-\text{COOH}$ with a group of the formula [VIII]:



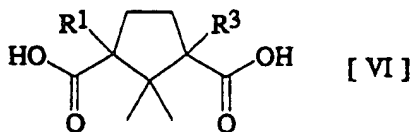
wherein the symbols are the same as defined above,
 5 by a conventional solid phase peptide synthesis method also known as Merrifield method (Journal of American Chemical Society 85, 2149-2154 (1963)), followed by the deprotection of amino group and carboxyl group by a conventional method.

10 R^{24} can be selected from a conventional protecting group for an amino group, for example, tert-butoxy-carbonyl group (BOC), benzyloxycarbonyl group (Cbz) and the like.

The solvent used for the Procedures (a) to (e) may be selected from any one which does not disturb the
 15 procedures, for example, THF, methanol, DMF, CH_2Cl_2 , or a mixture thereof.

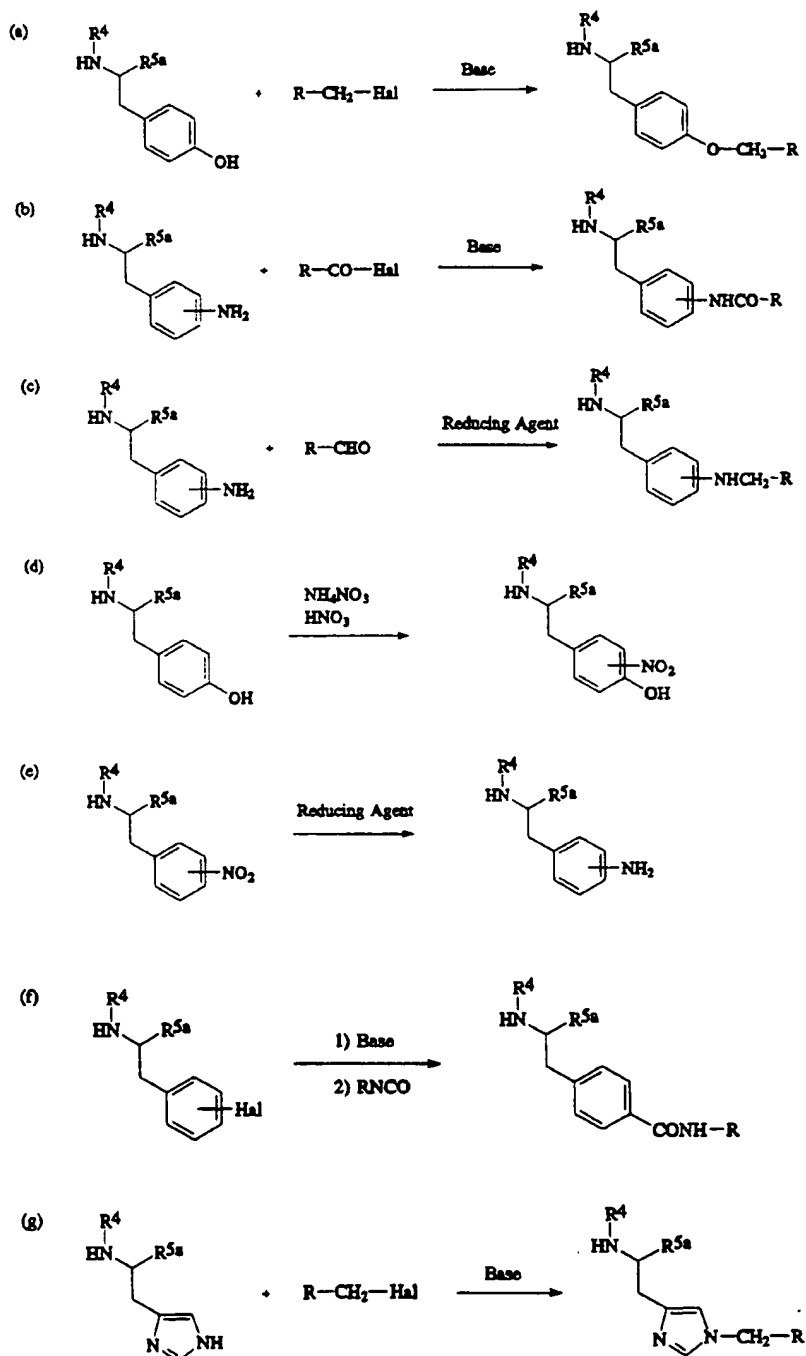
GENERAL DESCRIPTION FOR SYNTHESIS OF INTERMEDIATES

The compound [II] may be prepared by reacting a compound of the formula [VI]:



20 wherein the symbols are the same as defined above, in the presence of C_{1-6} alkanoyl halide (e.g., AcCl) and/or C_{1-6} alkanoyl anhydride (e.g., Ac_2O).

The compound [III-a] may be prepared by a conventional method, which is selected according to the types of the substituents, for example, by the following schemes:

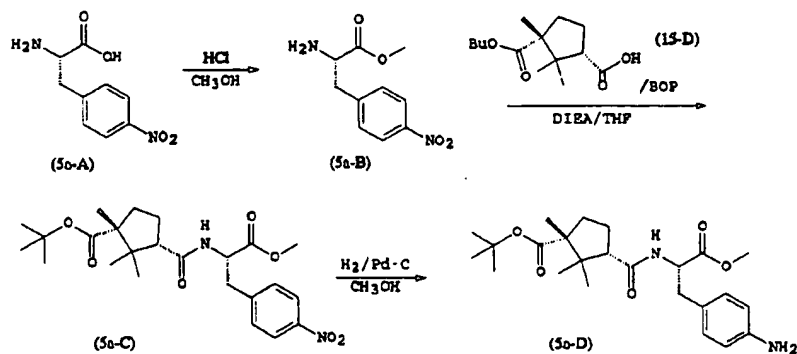


wherein R is (1) a substituted or unsubstituted monocyclic or bicyclic aryl group or (2) a substituted or unsubstituted monocyclic or bicyclic heteroaryl group, Hal is a halogen atom and other symbols are the same as defined above.

The compound [IV] may be prepared as shown in various locations of the present application, for example, in Schemes 7, 8, 9, 10 and 11.

The desired compound [I] of the present invention may also be prepared by the methods as shown in the following Schemes.

Scheme 5a



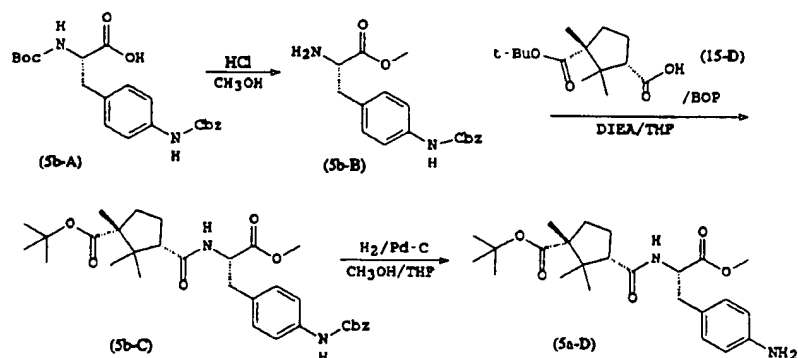
Commercially available (L)-p-nitroPhe-OH (5a-A) (50.6g, 240.6mmol) was dissolved in MeOH (250mL) and dry HCl was bubbled through the solution for 45 minutes at 0°C. The mixture was refluxed for 15 minutes and allowed to stand overnight. The HCl salt precipitated and the solid material was collected by filtration and washed with Et₂O (3 x 50mL). The solid methyl ester (5a-B) thus obtained was pale yellow (55.3g, 88%): mp = 215-218 °C (d).

The HCl salt of (L)-p-nitroPhe-OMe (5a-B) (5.2g, 19.8mmol) was dissolved in THF (30mL) containing DIEA (10.3mL, 59.4mmol). To this solution was added (1R-cis)-1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid
5 1-(1,1-dimethylethyl) ester (15-D) (5.1g, 19.8mmol) and BOP reagent (10.6g, 23.9mmol) and the solution was stirred under dry N₂ for 72 hours. Work-up of the coupling reaction was performed by the addition of 1N HCl (60 mL) and extraction with EtOAc (2 x 20 mL). The
10 combined organic phase was washed with saturated NaHCO₃ (20mL), then saturated LiCl (15 mL) and dried over Na₂SO₄. The solution was filtered, solvent evaporated and the residue chromatographed (SiO₂, gradient elution: 100% hexanes -> 50% EtOAc/hexanes) to provide the fully
15 protected intermediate (1S-cis)-N-[3-[(1,1-dimethylethoxy)-2,2,3-trimethylcyclopentyl]carbonyl]-4-nitro-L-phenylalanine methyl ester (5a-C) (7.1g, 77%):
¹H NMR (300 MHz, CDCl₃), δ 8.14 (2H), 7.35 (2H), 6.18 (1H), 4.99 (1H), 3.76 (3H), 3.34 (1H), 3.20 (1H), 2.62
20 (1H), 2.5-2.6 (2H), 2.1-2.2 (1H), 1.6-1.8 (1H), 1.4-1.5 (1H), 1.45 (9H), 1.25 (3H), 1.16 (3H), 0.81 (3H); ¹³C NMR (75 MHz, CDCl₃), δ 174.57, 172.44, 171.30, 146.69, 144.01, 129.87, 123.31, 79.89, 56.35, 53.98, 52.52, 52.24, 46.10, 37.38, 32.08, 27.72, 22.64, 22.27, 21.62,
25 20.40; ESMS (m/z) 463 (MH⁺).

The above compound, (5a-C) (2.7g, 5.77mmol), was dissolved in MeOH (40 mL) and degassed with N₂. To this solution was added 10 % Pd-C (250mg) and H₂ gas was bubbled through the resultant slurry for 15 minutes and
30 the reaction was stirred an additional 3 hours under an atmosphere of H₂. The mixture was filtered through celite and the celite washed with CH₃OH. The solvent was evaporated to afford Example 56 (5a-D) (2.49g, 100%):
¹H NMR (300 MHz, CDCl₃), δ 6.88 (2H), 6.64 (2H), 5.71
35 (1H), 4.82 (1H), 3.72 (3H), 3.0-3.1 (2H), 2.5-2.6 (2H),

2.1-2.2 (1H), 1.6-1.8 (1H), 1.4-1.5 (1H), 1.43 (9H),
1.21 (3H), 1.14 (3H), 0.80 (3H); ESMS (m/z) 433 (MH⁺).

Scheme 5b

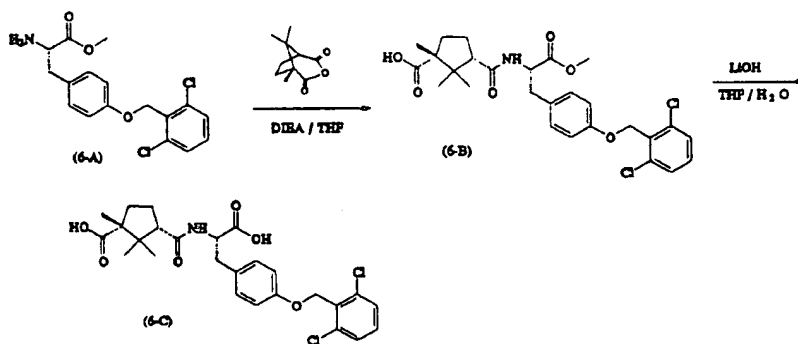


Commercially available Boc-(L)-Phe(4-N-Cbz)-OH
5 (5b-A) (6.2g, 14.9mmol) was dissolved in MeOH (20mL) and
dry HCl was bubbled through the solution for 10 minutes.
This mixture was stirred for 1 hour. The solvent was
evaporated and the solid material (5b-B) thus obtained
was washed with cold Et₂O (3 x 20 mL). This solid
10 material was dissolved in THF (25mL) containing DIEA
(7.8mL, 44.8mmol). To this solution was added (15-D)
(4.2g, 16.4mmol) and BOP reagent (7.9 g, 17.9 mmol) and
the solution was stirred under dry N₂ overnight. Work-up
of the coupling reaction was performed by the addition
15 of 1N HCl (60 mL) and extraction with EtOAc (2 x 50mL).
The combined organic phase was washed with saturated
LiCl (35mL) and dried over Na₂SO₄. The solution was
filtered, solvent evaporated and the residue
chromatographed (SiO₂, gradient elution: 100% hexanes ->
20 50% EtOAc/hexanes) to provide the fully protected
intermediate 4-benzyloxycarbonylamino-N-[(1S,3R)-3-
(tert-butoxycarbonyl)-2,2,3-trimethylcyclopentyl]carbonyl]-L-phenylalanine methyl
ester (5b-C) (6.5g, 77%): ¹H NMR (300 MHz, CDCl₃), δ
25 7.3-7.4 (6H), 7.17 (1H), 7.01 (2H), 5.80 (1H), 5.17

(2H), 4.86 (1H), 3.70 (3H), 3.06 (2H), 2.5-2.6 (2H), 2.1-2.2 (1H), 1.6-1.8 (1H), 1.4-1.5 (1H), 1.43 (9H), 1.21 (3H), 1.13 (3H), 0.80 (3H); ^{13}C NMR (75 MHz, CDCl_3), δ 174.88, 172.43, 172.06, 153.32, 136.98, 135.95, 130.55, 129.58, 128.46, 128.19, 128.15, 118.71, 80.05, 66.80, 56.54, 54.26, 52.98, 52.17, 46.25, 36.94, 32.21, 27.92, 22.81, 22.32, 21.82, 20.46; ESMS (m/z) 567 (MH^+).

The above compound, (5b-C) (5.74g, 10.13mmol), was dissolved in MeOH / THF (4:1, 50mL) and degassed with N_2 . To this solution was added 10 % Pd-C (500mg) and H_2 gas was bubbled through the resultant slurry for 1 hour. The reaction was stirred an additional 3 hours under an atmosphere of H_2 . The mixture was filtered through celite and the celite washed with CH_3OH . The solvent was evaporated to afford Example 56 (5a-D) (4.38g, 100%): ^1H NMR (300 MHz, CDCl_3), δ 6.90 (2H), 6.68 (2H), 5.73 (1H), 4.82 (1H), 3.72 (3H), 3.0-3.1 (2H), 2.5-2.6 (2H), 2.1-2.2 (1H), 1.6-1.8 (1H), 1.4-1.5 (1H), 1.43 (9H), 1.21 (3H), 1.14 (3H), 0.80 (3H); ESMS (m/z) 433 (MH^+).

20 Scheme 6

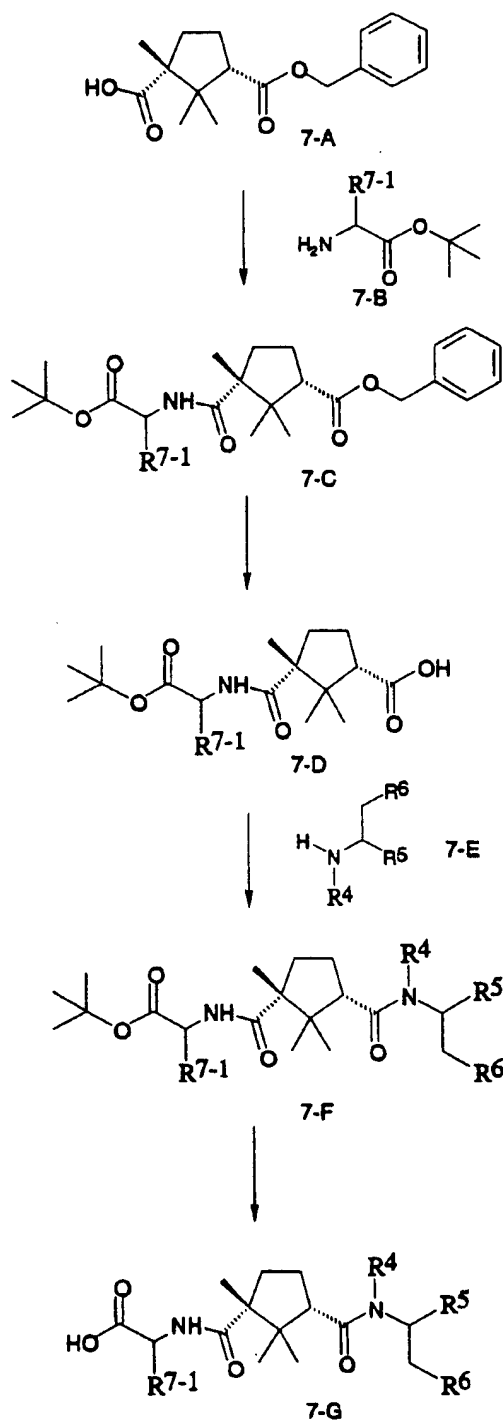


(1R)-Camphoric anhydride (243 mg, 1.33 mmol) was dissolved in THF (10mL) containing DIEA (1.2 mL, 6.67 mmol). To this solution O-2,6-dichlorobenzyl-L-tyrosine methyl ester (6-A) (618 mg, 1.58 mmol) was added and the solution stirred at 45°C for 1 h. The

reaction was cooled to room temperature and 1 N HCl (20 mL) was added. This was extracted with EtOAc (2 x 20 mL) and the combined organics were dried (Na_2SO_4), filtered, and the solvent removed in vacuo. The residue was chromatographed (SiO_2 , 10 % MeOH in CH_2Cl_2) to provide (6-B) (668 mg, 93 %) as a colorless oil: ^1H NMR (300 MHz, CDCl_3), (major isomer) δ 7.34 (d, 2H), 7.23 (dd, 1H), 7.04 (d, 2H), 6.9-7.0 (m, 2H), 5.85 (d, 1H), 5.23 (s, 2H), 4.88 (q, 1H), 3.73 (s, 3H), 3.0-3.2 (m, 2H), 2.5-2.6 (m, 2H), 2.2-2.3 (m, 1H), 1.7-1.8 (m, 1H), 1.4-1.5 (m, 1H), 1.23 (s, 3H), 1.22 (s, 3H), 0.84 (s, 3H); ESMS (m/z) 536 (MH^+).

(6-B) (570 mg, 1.06 mmol) was dissolved in THF (2mL). To this solution LiOH (89 mg, 3.72 mmol) was added in H_2O (2 mL) and the mixture stirred for 12 h at RT. The reaction was acidified with 1 N HCl (10 mL) and then extracted with EtOAc (2 x 20 mL). The combined organics were dried (Na_2SO_4), filtered, and the solvent removed in vacuo to provide Example 12 (6-C) (525 mg, 95 %) as a pale yellow foam: ^1H NMR (300 MHz, Acetone- d_6), (major isomer) δ 7.4-7.5 (m, 3H), 7.23 (d, 2H), 6.99 (d, 2H), 5.30 (d, 1H), 5.28 (s, 2H), 4.6-4.7 (m, 1H), 3.13 (dd, 1H), 2.97 (dd, 1H), 2.81 (t, 1H), 2.5-2.6 (m, 1H), 2.0-2.1 (m, 1H), 1.6-1.7 (m, 1H), 1.3-1.4 (m, 1H), 1.27 (s, 3H), 1.19 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (75 MHz, Acetone- d_6), (major isomer) δ 177.79, 173.99, 172.94, 158.53, 137.39, 133.18, 132.01, 131.23, 129.52, 115.24, 65.78, 56.75, 54.47, 53.67, 46.91, 37.19, 33.30, 23.44, 23.01, 22.38, 21.64; ESMS (m/z) 520 (M-H).

53

Scheme 7

Preparati n 7-A

Scheme 7, 7-A

Stereochemistry = 1S-cis

(Intermediate for Examples 181, 185, and 188)

- 5 (1R,3S)-Camphoric Acid 1-(1,1-Dimethylethyl)-3-phenylmethyl Ester ($C_{21}H_{30}O_4$)
- Benzyl bromide is eluted through neutral alumina (10mL in a 30mL sintered glass funnel) to give a colorless liquid (15mL, 126mmol) which is added to a stirred
- 10 solution of (1R, 3S)-camphoric acid 1-(1,1-dimethylethyl) ester (15-D) (30g, 117mmol), N,N-diisopropylethyl amine (24mL, 138mmol), and acetonitrile (90ml). After seven days, the mixture is filtered to give a white solid (diisopropylethyl amine
- 15 hydrobromide) and a yellow liquid which is placed in the freezer. After two days, the mixture is filtered (two 50mL diethyl ether rinses) to give a white solid (24g, 59% yield).
- 1H NMR:(300MHz, $CDCl_3$): δ 7.37-7.29(5H), 5.15(1H),
- 20 5.09(1H), 2.85-2.79(1H), 2.54-2.46(1H), 2.24-2.15(1H), 1.86-1.74(1H), 1.49-1.36(1H), 1.43(9H), 1.23(,3H), 1.15(3H), 0.78(3H); IR (nujol) 1737, 1724, 1717, 1346, 1272, 1259, 1219, 1210, 1162, 1124, 1116, 1084, 852, 737, 696 cm^{-1} ; MS (FAB) m/z (rel. intensity) 347
- 25 (M+H, 35), 348 (8), 347 (35), 292 (8), 291 (43), 273 (12), 109 (13), 92 (9), 91 (99), 57 (30), 41 (9); HRMS (FAB) calcd for $C_{21}H_{30}O_4 + H^+$ 347.2222, found 347.2232; Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; Found: C, 72.79; H, 8.90.
- 30 (1R,3S)-Camphoric Acid 3-Phenylmethyl Ester (7-A) ($C_{17}H_{22}O_4$)
- To (1R,3S)-camphoric Acid 1-(1,1-Dimethylethyl)-3-phenylmethyl ester (24g, 69mmol) is added
- trifluoroacetic acid (15mL). After stirring for two
- 35 days, the solution is evaporated in vacuo to give a

pale yellow oil which is dissolved in toluene (250mL) and shaken with water (6X100mL). Evaporation of the toluene gave a colorless oil which slowly crystallizes to give 7-A as an oily, white solid (16.4g, 81% yield).

¹H-NMR: (300MHz, CDCl₃): δ 7.38-7.16(5H), 5.17(1H), 5.11(1H), 2.87(1H), 2.60-2.49(1H), 2.30-2.21(1H), 1.91-1.80(1H), 1.57-1.48(1H), 1.27(3H), 1.25(3H), 0.84(3H); IR (liq.) 3067, 3034, 2972, 2888, 1732, 1696, 1457, 1378, 1285, 1231, 1212, 1166, 1124, 752, 698cm⁻¹; MS (FAB) m/z (rel. intensity) 291 (M+H, 44), 391 (5), 292 (8), 291 (44), 273 (6), 245 (4), 155 (3), 109 (10), 92 (9), 91 (99), 41 (3); HRMS (FAB) m/z calcd for C₁₇H₂₂O₄ +H⁺ 291.1596, found 291.1603; Anal. Calcd for C₁₇H₂₂O₄: C, 70.32; H, 7.64; Found: C, 70.21; H, 7.89.

Preparation 7-C-1

Scheme 7, 7-C: wherein R⁷⁻¹ = H

Stereochemistry = 1S-cis

(1R-cis)-N-[[3-[(phenylmethoxy)carbonyl]-1,2,2-trimethylcyclopentyl]carbonyl]glycine (1,1-dimethylethyl) ester (7-C-1) (C₂₃H₃₃NO₅)

To (1R,3S)-camphoric acid 3-phenylmethyl ester 7-A (0.736g, 2.53mmol) in dry DMF (5mL) is added diisopropylethyl amine (3mL, 17.2mmol) and HATU (1.05g, 2.76mmol). Thirty minutes later, 7-B (R⁷⁻¹ = H) hydrochloride (0.855g, 5.10mmol) is added. After overnight stirring, the mixture is evaporated to dryness (in vacuo/ N₂ flow) and then mixed with toluene (50mL) and THF (50mL) and washed with water (2x50mL), 1N HCl (50mL), and water (4x50mL). The organic layer is then evaporated to dryness, giving 7-C (R⁷⁻¹ = H) as an off-white solid (0.9g, 90%).

¹H NMR (300MHz, CDCl₃) δ 7.37-7.15 (5H), 6.05 (1H), 5.17-5.08 (2H), 3.99-3.82 (2H), 2.89-2.83 (1H), 2.51-2.40 (1H), 2.29-2.22 (1H), 1.94-1.80 (1H), 1.59-1.51 (1H), 1.47 (9H), 1.31 (3H), 1.21 (3H), 0.78 (3H). MS (ES+) m/z
5 404.1 (parent).

Preparation 7-D

Scheme 7, 7-D: wherein R⁷⁻¹ = H

Stereochemistry = 1*S*-cis

(1*R*-cis)-N-[[3-carboxy-1,2,2-trimethylcyclopentyl]carbonyl]glycine (1,1-dimethylethyl) ester (7-D-1) (C₁₆H₂₇NO₅)
10 Ester 7-C (R⁷⁻¹ = H, 0.97g, 2.4mmol) in THF (12mL) and ethanol (6mL) is shaken with 10%Pd/C (0.115g) in a Parr bottle under an H₂ (38psi) atmosphere. After 8
15 hours, the bottle is removed from the shaker and filtered through Celite (with 3X30mL ethanol rinses). The filtrate is evaporated to dryness, giving 7-D (R⁷⁻¹ = H) as a thick, colorless oil (0.6g, 79% yield).
¹H NMR (300MHz, CDCl₃) δ 6.13 (1H), 4.0-3.84 (2H),
20 2.86-2.80 (1H), 2.49-2.39 (1H), 2.27-2.17 (1H), 1.94-1.80 (1H), 1.60-1.52 (1H), 1.46 (9H), 1.34 (3H), 1.22 (3H), 0.88 (3H); IR (liq.) 3385, 2976, 2940, 2887, 1732, 1644, 1528, 1478, 1459, 1405, 1394, 1369, 1277, 1227, 1158 cm⁻¹; MS (FAB) m/z (rel. intensity) 314
25 (M+H, 99), 315 (18), 314 (99), 258 (51), 109 (22), 95 (9), 76 (20), 69 (12), 57 (28), 55 (12), 41 (14).
HRMS (FAB) m/z calcd for C₁₆H₂₇NO₅ +H⁺ 314.1967, found 314.1974; Anal. Calcd for C₁₆H₂₇NO₅ :
C, 61.32; H, 8.68; N, 4.47; Found: C, 61.70; H,
30 8.86; N, 4.14; Melt Solvate: 3.9% Ethanol.

Preparation 7-F-1

Scheme 7, 7-F: wherein $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2CH_3$,

$R^6 = 4-[(2,6-Dichlorobenzoyl)amino]$ phenyl

Stereochemistry = (1S-cis) - L

- 5 (1S-cis) -N-[[3-[[[(1,1-dimethylethoxycarbonylmethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester (7-F-1) ($C_{33}H_{41}Cl_2N_3O_7$)
- 10 (1R-cis) -N-[[3-carboxy-1,2,2-trimethylcyclopentyl]carbonyl]glycine (1,1-dimethylethyl) ester 7-D ($R^{7-1} = H$, 0.356g, 1.14mmol) is dissolved in methylene chloride (6mL), under N_2 in a round bottom flask, and is cooled in an ice water
- 15 bath. To this stirred solution is added N,N-diisopropylethylamine (1mL, 5.7mmol), EDC (0.242g, 1.26mmol), HOBt (0.181g, 1.34mmol), and 4-N,N-dimethylaminopyridine (0.016g, 0.13mmol) followed 30 minutes later by 4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester hydrochloride 7-E-1·HCl
- 20 (7E: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-dichlorobenzoyl)amino]$ phenyl, Stereochemistry = S) (0.487g, 1.2mmol). After two days of stirring (the ice bath is allowed to melt), the reaction mixture is
- 25 evaporated to dryness and then partitioned between THF (100mL), diethyl ether (50mL), and water (50mL). The organic layer is washed with water (3X50mL), aqueous HCl (0.5N, cold, 3X30mL), aqueous sodium bicarbonate (1X50mL), water (3X30mL, to pH7), and then evaporated
- 30 to dryness, giving 7-F ($R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]$ phenyl, Stereochemistry = (1S-cis)-L) as a white solid (0.63g, 80%yield).
- 35 1H NMR (300MHz, $CDCl_3$) δ 7.57(2H), 7.38-7.26(3H), 7.10(2H), 6.07(1H), 5.80(1H), 4.89(1H), 3.97-3.74(2H),

3.21-3.05 (2H), 2.58-2.52 (1H), 2.45-2.35 (1H),
 2.30-2.18 (1H), 1.90-1.75 (1H), 1.58-1.50 (1H), 1.46 (9H),
 1.30 (3H), 1.20 (3H), 0.79 (3H); IR (nujol) 1739, 1668,
 1643, 1609, 1560, 1538, 1516, 1431, 1414, 1327, 1288,
 5 1256, 1235, 1195, 1161 cm^{-1} ; MS (FAB) m/z (rel.
 intensity) 662 (M+H, 84), 664 (58), 663 (39), 662
 (84), 533 (39), 531 (55), 240 (58), 194 (37), 173
 (41), 109 (99), 57 (44); HRMS (FAB) m/z calcd for
 $\text{C}_{33}\text{H}_{41}\text{Cl}_2\text{N}_3\text{O}_7 + \text{H}^+$ 662.2399, found 662.2410.

10

Preparation 7-G-1

Scheme 7, 7-G: wherein $\text{R}^{7-1} = \text{H}$, $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$,
 $\text{R}^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]\text{-phenyl}$
 Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[(Carboxymethyl)amino]carbonyl]-
 15 2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-
 dichlorobenzoyl)amino]-L-phenylalanine methyl ester
 (7-G-1) ($\text{C}_{29}\text{H}_{33}\text{Cl}_2\text{N}_3\text{O}_7$)

(1S-cis)-N-[[3-[[[(1,1-
 dimethylethyloxycarbonylmethyl)amino]carbonyl]-2,2,3-
 20 trimethylcyclopentyl]carbonyl]-4-[(2,6-
 dichlorobenzoyl)amino]-L-phenylalanine methyl ester
 7-F ($\text{R}^{7-1} = \text{H}$, $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$, $\text{R}^6 = 4-[(2,6\text{-}$
 Dichlorobenzoyl)amino]-phenyl, Stereochemistry =
 (1S-cis)-L, 0.802g, 1.21mmol) is stirred overnight in
 25 trifluoroacetic acid (3mL). The solution is then
 diluted with toluene (5mL) and evaporated to dryness
 in vacuo to give an off white solid which was
 recrystallized from chloroform/ diethyl ether to give
 7-G ($\text{R}^{7-1} = \text{H}$, $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$, $\text{R}^6 = 4-[(2,6\text{-}$
 30 Dichlorobenzoyl)amino]-phenyl, Stereochemistry =
 (1S-cis)-L as a white solid (0.7g, 90% yield).
 $^1\text{H-NMR}$: (300MHz, DMSO-d_6): δ 10.68 (1H), 7.92 (2H), 7.58-
 7.44 (3H), 7.19 (2H), 4.53-4.45 (1H), 3.75-3.62 (2H),
 3.58 (3H), 3.03-2.85 (2H), 2.68-2.62 (1H), 2.40-2.28 (1H),

1.98-1.81(1H), 1.70-1.50(1H), 1.30-1.25(1H), 1.17(3H),
1.09(3H).

Preparation of Example 181

Scheme 7, 7-G: wherein $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2H$, $R^6 = 4-$

5 [(2,6-Dichlorobenzoyl)amino]phenyl,

Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[(Carboxymethyl)amino]carbonyl]-2,2,3-
trimethylcyclopentyl]carbonyl]-4-[(2,6-
dichlorobenzoyl)amino]-L-phenylalanine (Example 181)

10 ($C_{28}H_{31}Cl_2N_3O_7$)

(1S-cis)-N-[[3-[[[(Carboxymethyl)amino]carbonyl]-2,2,3-
trimethylcyclopentenyl]carbonyl]-4-[(2,6-
dichlorobenzoyl)amino]-L-phenylalanine methyl ester

15 (7-G-1) (0.7g, 1.15mmol) is dissolved in methanol
(12mL). To this is added a mixture of $LiOH \cdot H_2O$
(0.243g, 5.8mmol), aqueous H_2O_2 (30%, 2mL), and H_2O
(2mL). After overnight stirring, the reaction mixture
is diluted with water (50mL), and evaporated (room
temperature, in vacuo/ N_2 flow) until the methanol is
20 gone. The aqueous solution is then transferred to a
separatory funnel and shaken with diethyl ether
(2X20mL). The aqueous layer is then evaporated, to
remove residual diethyl ether, and cooled in an ice
water bath. The stirred solution is then brought to
25 pH3-4 using aqueous HCl (1N). The resultant
precipitate is isolated by suction filtration (with
water washes) to give Example 181 as a white solid (
0.4g, 58% yield)

1H -NMR: (300MHz, DMSO- d_6): δ 12.45(1H), 10.6(1H),
30 7.74(2H), 7.57-7.44(3H), 7.20(2H), 4.48-4.40(1H),
3.65(2H), 2.94(2H), 2.64(1H), 2.35(1H), 1.90(1H),
1.58(1H), 1.29(1H), 1.18(3H), 1.08(3H), 0.60(3H); IR
(nujol) 3124, 3088, 3078, 1738, 1666, 1628, 1612,
1588, 1563, 1552, 1521, 1429, 1334, 1197, 1170 cm^{-1} ; MS
35 (FAB) m/z (rel. intensity) 592 (M+H, 99), 595 (20),

594 (69), 593 (41), 592 (99), 519 (25), 517 (38), 240 (55), 175 (23), 173 (33), 109 (64); HRMS (FAB) m/z calcd for $C_{28}H_{31}Cl_2N_3O_7 + H^+$ 592.1617, found 592.1606; Anal. Calcd for $C_{28}H_{31}Cl_2N_3O_7$: C, 56.76; H, 5.27; N, 7.09; Found: C, 54.92; H, 5.41; N, 6.91; KF Water: 3.05% H_2O .

Preparation 7-F-2

Scheme 7, 7-F: wherein wherein $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]$ -phenyl

10

Stereochemistry = (1S-cis)-L

[1S-cis]-O-(((2,6-Dichlorophenyl)methyl))-N-[[3-[[[(1,1-diemethylethoxy)carbonylmethyl)amino]-carbonyl]-2,2,3-trimethylcyclopentyl)carbonyl]-L-tyrosine methyl ester (7-F-2) ($C_{33}H_{42}Cl_2N_2O_7$)

15

is prepared from 7-D ($R^{7-1} = H$ and O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester 7-E-2 (7-E: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]$ phenyl, Stereochemistry = S) as taught by Scheme 7.

20

1H NMR ($CDCl_3$) δ 7.39-6.94 (7H), 6.09 (1H), 5.78 (1H), 5.25 (2H), 4.87 (1H), 3.90 (2H), 3.74 (3H), 3.09 (2H), 2.59-2.20 (3H), 1.80 (1H), 1.56 (1H), 1.47 (9H), 1.30 (3H), 1.26 (3H), 0.81 (3H); IR (mull) 3327, 1762, 1741, 1664, 1637, 1538, 1512, 1440, 1241, 1229, 1206,

25

1198, 1174, 1156, 1022 cm^{-1} ; MS (FAB) m/z (rel. intensity) 649 (M+H, 50), 651 (34), 649 (50), 518 (21), 296 (23), 240 (44), 194 (28), 161 (26), 159 (41), 109 (99), 57 (37).

Preparation 7-G-2

Scheme 7, 7-G: wherein $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 =$

4-[(2,6-Dichlorophenyl)methoxy]phenyl

Stereochemistry = (1S-cis)-L

- 5 [1S-cis]-O-[(2,6-Dichlorophenyl)methyl]-N-[[3-
 [[(Carboxymethyl)amino]carbonyl]-2,2,3-
 trimethylcyclopentyl]carbonyl]-L-tyrosine methyl ester
 (7-G-2) ($C_{29}H_{34}Cl_2N_2O_7$) is prepared from 7-F-2 as taught
 by Scheme 7.

10 1H NMR($CDCl_3$) δ 8.14 (1H), 7.37-6.93 (7H), 6.51 (1H),
 6.02 (1H), 5.24 (2H), 4.85 (1H), 4.02 (2H), 3.73 (3H),
 3.09 (2H), 2.57 (1H), 2.41 (1H), 2.25 (1H), 1.84 (1H),
 1.56 (1H), 1.26 (3H), 1.20 (3H), 0.79 (3H); MS(ES+) m/z
 592.9.

15 Preparation of Example 185

Scheme 7, 7-G: wherein $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2H$, $R^6 =$

4-[(2,6-Dichlorophenyl)methoxy]phenyl,

Stereochemistry = (1S-cis) - L

- (1S-cis)-N-[[3-[[[(Carboxymethyl)amino]carbonyl]-2,2,3-
 20 trimethylcyclopentyl]carbonyl]-O-[(2,6-
 dichlorophenyl)methyl]-L-tyrosine (Example 185)

($C_{28}H_{32}Cl_2N_2O_7$) is prepared from 7-G-2 ($R^{7-1} = H$, $R^4 = H$, R^5
 = CO_2CH_3 , $R^6 =$ 4-[(2,6-Dichlorophenyl)methoxy]-phenyl,
 Stereochemistry = S) as taught by Scheme 7.

- 25 1H NMR(300MHz, DMSO- d_6) 7.8-6.9 (9H), 5.18 (2H), 4.42 (1H),
 3.8-3.6 (2H), 3.02-2.82 (2H), 2.65 (1H), 2.38 (1H),
 1.91 (1H), 1.58 (1H), 1.30 (1H), 1.19 (3H), 1.10 (3H),
 0.61 (3H); IR (nujol) 3409, 1733, 1645, 1612, 1585, 1564,
 1511, 1439, 1297, 1239, 1197, 1179, 1018, 786, 770 cm^{-1}
 30 1 ; MS (FAB) m/z (rel. intensity) 579 (M+H, 99), 582 (22),
 581 (67), 580 (44), 579 (99), 578 (21), 240 (34), 161
 (21), 159 (34), 109 (46), 91 (37); HRMS (FAB) m/z calcd
 for $C_{28}H_{32}Cl_2N_2O_7$ +H $^+$ 579.1664, found 579.1667.

Preparation 7-C-2

Scheme 7, 7-C: wherein $R^{7-1} = CH_3$ Stereochemistry = [1S-[1 α ,3 α (R*)]]

[1S-[1 α ,3 α (R*)]]-3-[[[1-(1,1-Dimethylethoxycarbonyl)ethyl]amino]carbonyl]-2,2,3-trimethylcyclopentanecarboxylic acid [phenyl(methyl)] ester (7-C-2) ($C_{24}H_{35}NO_5$) is prepared from 7-A and 7-B. ($R^{7-1} = CH_3$, Stereochemistry = s) as taught by Scheme 7. 1H NMR(300MHz, $CDCl_3$) δ 7.37-7.16 (5H), 6.18 (1H), 5.12 (2H), 4.41 (1H), 2.84 (1H), 2.46 (1H), 2.28 (1H), 1.87 (1H), 1.52 (1H), 1.51 (9H), 1.35 (3H), 1.28 (3H), 1.20 (3H), 0.78 (3H). MS(ES+) m/z 455.1

Preparation 7-D-2

Scheme 7, 7-D: wherein wherein $R^{7-1} = CH_3$ 15 Stereochemistry = [1S-[1 α ,3 α (R*)]]

[1S-[1 α ,3 α (R*)]]-3-[[[1-(1,1-Dimethylethoxycarbonyl)ethyl]amino]carbonyl]-2,2,3-trimethylcyclopentanecarboxylic acid (7-D-2) ($C_{17}H_{29}NO_5$) is prepared from 7-C-2 as taught by Scheme 7. 1H NMR(300MHz, $CDCl_3$) δ 6.28 (1H), 4.44 (1H), 2.86 (1H), 2.43 (1H), 2.23 (1H), 1.93 (1H), 1.56 (1H), 1.47 (9H), 1.36 (3H), 1.31 (3H), 1.22 (3H), 0.90 (3H); MS(ES-) m/z 326.1.

Preparation 7-F-3

25 Scheme 7, 7-F: wherein $R^{7-1} = CH_3$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]phenyl$
Stereochemistry = [1S-[1 α ,3 α (R*)]]

[1S-[1 α ,3 α (R*)]]-O-[(2,6-Dichlorophenyl)methyl]-N-[[[1-(1,1-dimethylethoxycarbonyl)ethyl]amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-L-tyrosine methyl ester (7-F-3) ($C_{34}H_{44}Cl_2N_2O_7$) is prepared from 7-D-2 and 7-E-2

(7E: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-$
 Dichlorophenyl)methoxy]phenyl) as taught by Scheme 7.
 1H NMR(300MHz, $CDCl_3$) δ 7.38-6.93(7H), 6.20 (1H),
 5.77(1H), 5.25 (2H), 4.87 (1H), 4.42 (1H), 3.73 (3H),
 5 3.09 (2H), 2.44(2H), 1.76 (2H), 1.52(1H), 1.46 (9H),
 1.35(3H), 1.27(3H), 1.20(3H), 0.80(3H). IR (nujol)
 1739, 1654, 1612, 1585, 1565, 1511, 1439, 1344, 1300,
 1240, 1198, 1177, 1154, 1017, 768 cm^{-1} . MS (FAB) m/z
 (rel. intensity) 663 (M+H, 82), 665 (60), 664 (37),
 10 663 (82), 518 (27), 254 (51), 208 (24), 161 (28), 159
 (45), 109 (99), 57 (33).

Preparation 7-G-3

Scheme 7, 7-G: wherein $R^{7-1} = CH_3$, $R^4 = H$, $R^5 = CO_2CH_3$, R^6
 $= 4-[(2,6-Dichlorophenyl)methoxy]phenyl$
 15 Stereochemistry = [1S-[1 α ,3 α (R')]]-L

[1S-[1 α ,3 α (R')]]-O-[(2,6-Dichlorophenyl)methyl]-N-[[3-
 [[(1-Carboxyethyl)amino]carbonyl]-2,2,3-
 trimethylcyclopentyl]carbonyl]-L-tyrosine methyl ester
 (7-G-3) ($C_{30}H_{36}Cl_2N_2O_7$) is prepared from 7-F-3 as taught
 20 by Scheme 7.

1H NMR(300MHZ, $CDCl_3$) δ 10.55 (1H), 7.38-6.94 (7H).
 6.47(1H), 6.12 (1H), 5.25 (2H), 4.87(2H), 4.55(1H),
 3.75(3H), 3.10(2H), 2.60 (1H), 2.41 (1H), 2.25 (1H),
 1.87(1H), 1.58 (1H), 1.46(3H), 1.24(3H), 1.21 (3H).,
 25 0.78 (3H); MS(ES+) m/z 606.8

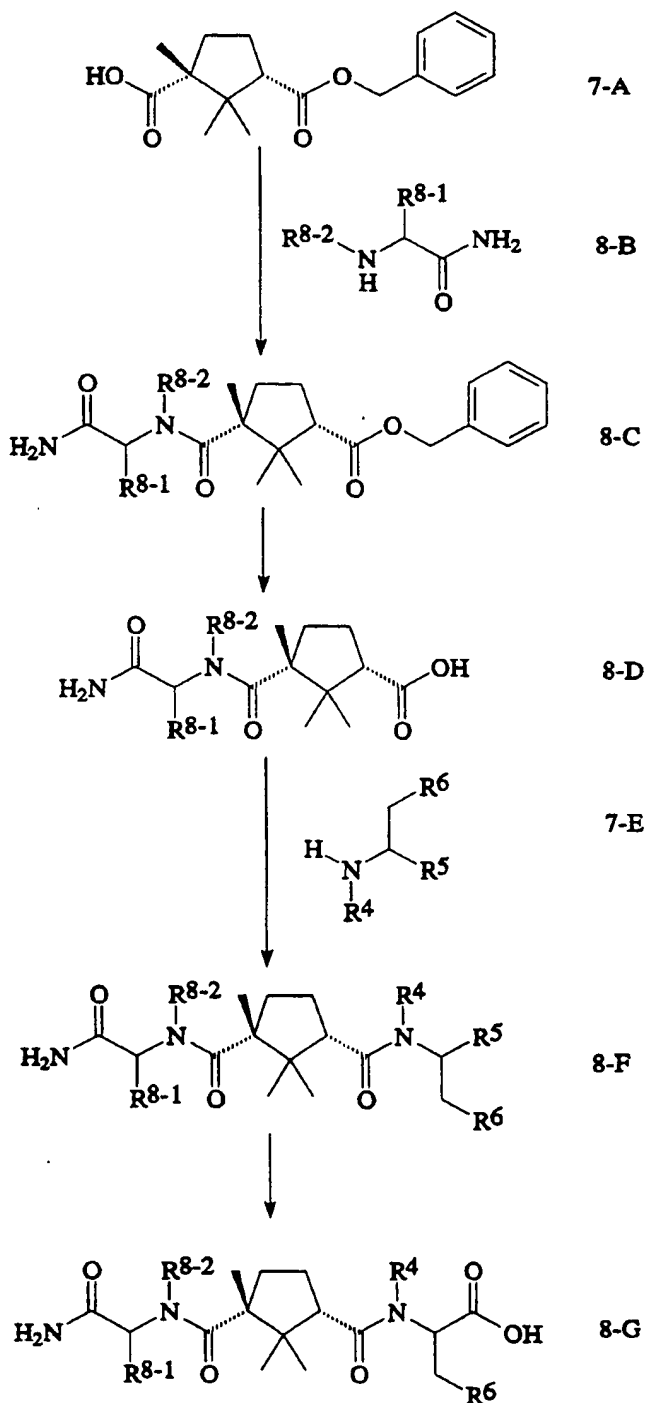
Preparation of Example 188

Scheme 7, 7-G: wherein $R^{7-1} = CH_3$, $R^4 = H$, $R^5 = CO_2H$, $R^6 =$
4-[(2,6-Dichlorophenyl)methoxy]phenyl,
Stereochemistry = [1S-[1 α ,3 α (R*)]]

- 5 [1S-[1 α ,3 α (R*)]]-N-[[3-[(1-Carboxyethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine (C₂₉H₃₄Cl₂N₂O₇) is prepared from 7-G-3 as taught by Scheme 7.
- 10 ¹H NMR(300MHz, DMSO-d₆) 7.71(1H), 7.54-7.43(3H), 7.28(1H), 7.16(2H), 6.93(2H), 5.16(2H), 4.40(1H), 4.16(1H), 3.02-2.80(2H), 2.63(1H), 2.35(1H), 1.86(1H), 1.54(1H), 1.35-1.23(4H), 1.14(3H), 1.08(3H), 0.59(3H); IR (nujol) 3427, 3031, 1731, 1645, 1612, 1585, 1565,
- 15 1512, 1439, 1297, 1239, 1230, 1197, 1179, 1017 cm⁻¹; MS (FAB) m/z (rel. intensity) 593 (M+H, 99), 596 (22), 595 (69), 594 (43), 593 (99), 592 (17), 504 (22), 254 (63), 161 (44), 159 (40), 109 (72).

Scheme 8

R^{8-1} is defined in the same manner as R^{7-1} to include amino acids included in R^2 definition; R^{8-2} is proton or together with R^{8-1} cyclic amino acid.



Preparation 8-C-1

Scheme 8, 8-C: wherein: $R^{8-1} = H$, $R^{8-2} = H$ Stereochemistry = 1*S*-cis

(1*S*-cis)-*N*-[[1-[(phenylmethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]glycine amide (8-C-1)
($C_{19}H_{26}N_2O_4$)

A solution of (1*R*-cis)-[3-(phenylmethoxy)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid (7-A) (1g, 3.44mmol) in dry DMF is cooled in an ice water bath and diisopropylethylamine (1.77g, 13.76mmol, 2.39mL), HATU (1.35g, 3.55mmol), and 8-B ($R^{8-1} = H$, $R^{8-2} = H$) (0.38g, 3.44mmol) are added in order. The mixture is allowed to stir for 48 hours as the ice melts and the solution warms to room temperature. The solution is cast into methylene chloride (0.25L) and 1N aq. NaOH (0.25L). The organic phase is separated and washed in order with 1N aq. HCl (0.25L), water (5X0.25L), and brine (0.25L). The organic phase is dried and concentrated in vacuo to give the crude amide as an ivory powder. The crude amide is recrystallized from hexanes-chloroform to furnish the target amide 8-C ($R^{8-1} = H$, $R^{8-2} = H$) as a fine, free flowing, white powder.

MP: 163-164°C; 1H -NMR (300MHz, $CDCl_3$): δ 7.25-7.40(5H), 6.36(1H), 6.08(1H), 5.33(3H), 5.15(1H), 5.10(1H), 3.93(2H), 2.85(1H), 2.43(1H), 2.27(1H), 1.40-1.65(2H), 1.30(3H), 1.21(3H), 0.76(3H); IR (nujol) 3383, 3361, 3184, 2924, 1766, 1710, 1684, 1626, 1527, 1402, 1253, 1166, 753 cm^{-1} ; MS (EI) m/z (rel intensity) 346(M+, 4), 329(2), 273(3), 255(3), 239(3), 211(6), 153(11), 109(17), 91(base); Anal. calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09; Found: C, 65.94; H, 7.65; N, 8.09.

Preparation 8-D-1

Scheme 8, 8-D: wherein: $R^{8-1} = H$, $R^{8-2} = H$

Stereochemistry = 1S-cis

5 (1R-cis)-N-[[3-carboxy-1,2,2-trimethylcyclopentyl]-
carbonyl]glycine amide (8-D-1) ($C_{12}H_{20}N_2O_4$)

A solution of 8-C ($R^{8-1} = H$, $R^{8-2} = H$) (3.46g, 100mmol) in THF (225mL), containing 10% Pd/C (1.14g), is hydrogenated under 50psi of hydrogen for 12 hours. The catalyst is removed by filtration through a cake of Celite, the filter cake is rinsed with THF (100mL), and the combined filtrates are concentrated in vacuo to give the crude product as a white foam. The crude material is recrystallized from hexanes-THF to afford the target compound 8-D ($R^{8-1} = H$, $R^{8-2} = H$) (2.4g, 94%) as fine white needles.

15 MP: 86-87°C; 1H -NMR (300MHz, DMSO- d_6): δ 12.00(1H), 7.28(1H), 7.13(1H), 6.92(1H), 3.56(2H), 2.67(1H), 2.34(1H), 1.97(1H), 1.72(1H), 1.36(1H), 1.19(3H), 1.09(3H), 0.68(3H); IR(nujol) 3496, 3391, 3189, 2924, 1729, 1705, 1686, 1623, 1519, 1401, 1280, 1245, 1200, 665 cm^{-1} ; MS(EI) m/z (rel intensity) 238(2), 221(6), 195(base), 138(26), 109(81), 95(67); Anal. calcd for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.86; N, 10.93; Found: C, 55.90; H, 8.05; N, 10.50.

25

Preparation 8-F-1

Scheme 8, 8-F: wherein $R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$, Stereochemistry = (1S-cis) - L

30 (1S-cis)-N-[[3-[[[(2-Amino-2-oxoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester ($C_{29}H_{34}Cl_2N_4O_6$)

To 8-D ($R^{8-1} = H$, $R^{8-2} = H$) (1.03g, 4mmol) in dry DMF (25mL), cooled in a an ice-water bath, is added in

order, diisopropylethylamine (2.07g, 16mmol, 2.8mL),
 4-(2,6-dichlorobenzamido)-L-phenylalanine methyl ester
 hydrochloride 7-E-1·HCl (7-E: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 =$
 4-[(2,6-dichlorobenzoyl)amino]phenyl) (1.48g, 4mmol),
 5 and HATU (1.49g, 4.2mmol). The mixture is stirred for
 48 hours as the ice melts and the mixture warms to
 room temperature. The solution is cast into ethyl
 acetate (1L) and this solution is washed successively
 with 1N aq. HCl (1L), 1N aq. NaOH (1L), water (4X1L),
 10 and brine (1L). The organic phase is separated, dried
 (Na_2SO_4), and concentrated in vacuo to give the desired
 product 8-F ($R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 =$
 4-[(2,6-dichlorobenzoyl)amino]phenyl) (1.12g, 42%) as
 a fine, white powder.
 15 MP: 232-233°C; 1H -NMR (300MHz, DMSO- d_6): δ 10.75(1H),
 7.94(1H), 7.45-7.70(5H), 7.35(1H), 7.19(2H), 7.13(1H),
 6.92(1H), 4.81(1H), 3.57(3H), 3.55(2H), 2.92(2H),
 2.64(1H), 2.34(1H), 1.88(1H), 1.62(1H), 1.30(1H),
 1.16(3H), 1.07(3H), 0.58(3H); IR (nujol): 3344, 3251,
 20 3194, 3126, 3072, 2924, 1743, 1699, 1669, 1652, 1623,
 1528, 1432, 1328, 799 cm^{-1} ; MS (FAB): m/z (rel.
 intensity) 605(M+2H, base), 531(28), 503(2), 367(7),
 349(17), 256(10), 239(66), 194(31), 173(37), 137(12),
 109(83); Anal. calcd for $C_{29}H_{34}Cl_2N_4O_6 \cdot 0.3H_2O$: C, 57.02;
 25 H, 5.71; N, 9.17; Found: C, 57.01; H, 5.86; N,
 8.89.

Preparation of Example 180

Scheme 8, 8-G: wherein $R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$,
 $R^5 = CO_2H$, $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$,
 30 Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[(2-Amino-2-oxoethyl)amino]-carbonyl]-
 2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-
 dichlorobenzoyl)amino]-L-phenylalanine (Example 180)
 ($C_{28}H_{32}Cl_2N_4O_6$)

To 8-F ($R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-dichlorobenzoyl)amino]-phenyl$) (1.05g, 1.7mmol), dissolved in methanol (30mL), is added a solution of $LiOH \cdot 2H_2O$ (0.32g, 7.65mmol) in water (10mL), dropwise over 15 minutes. The mixture stirs for 18 hours at room temperature and the pH is then adjusted to ca. 7 by the careful addition of 1N aq. HCl. The majority of the methanol, is removed in vacuo and the pH of the resulting solution is adjusted to ca. 2 with 1N aq. HCl. The resulting flocculent white precipitate is isolated by filtration and dried. The solid is crushed and washed with water (2X10mL) and dried in vacuo at 50°C to give 0.97g (97%) of 8-G ($R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$, $R^5 = CO_2H$, $R^6 = 4-[(2,6-dichlorobenzoyl)amino]-phenyl$) as a white, powdery solid.

MP: 203-205°C; 1H NMR (300MHz, DMSO- d_6): 12.51(1H), 10.70(1H), 7.75(1H), 7.45-7.57(3H), 7.33(1H), 7.20(2H), 7.11(1H), 6.92(1H), 4.43(1H), 3.63(1H), 3.47(2H), 3.30(2H), 3.01(1H), 2.84(1H), 2.31(1H), 1.87(1H), 1.55(1H), 1.31(1H), 1.17(3H), 1.08(3H), 0.59(3H); IR (nujol): 3511, 3325, 3128, 3082, 2868, 1722, 1697, 1664, 1614, 1555, 1537, 1417, 1337, 1246, 799 cm^{-1} ; MS (FAB) m/z (rel. intensity) 591(M+H, base), 517(32), 335(26), 239(32), 173(39), 109(63), 57(80); HRMS (FAB) m/z calcd for $C_{28}H_{31}Cl_2N_4O_6 + H^+$ 591.1777, found 591.1747.

Preparation 8-F-2

Scheme 8, 8-F: wherein $R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]phenyl$

Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[(2-Amino-2-oxoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester (8-F-2)

(C₂₉H₃₅Cl₂N₃O₆) is prepared from 8-D (R⁸⁻¹ = H, R⁸⁻² = H) and 7-E-2 (R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-[(2,6-dichlorophenyl)methoxy]phenyl) as taught by Scheme 8. ¹H NMR(CDCl₃) δ 7.37-6.93 (7H), 6.54 (1H), 6.40 (1H), 5.82 (1H), 5.60 (1H), 5.24 (2H), 4.85 (1H), 3.93 (2H), 3.73 (3H), 3.09 (2H), 2.54 (1H), 2.40 (1H), 2.23 (1H), 1.78 (1H), 1.52 (1H), 1.27 (3H), 1.20 (3H), 0.78 (3H); MS(ES+) m/z 591.9.

Preparation of Example 187

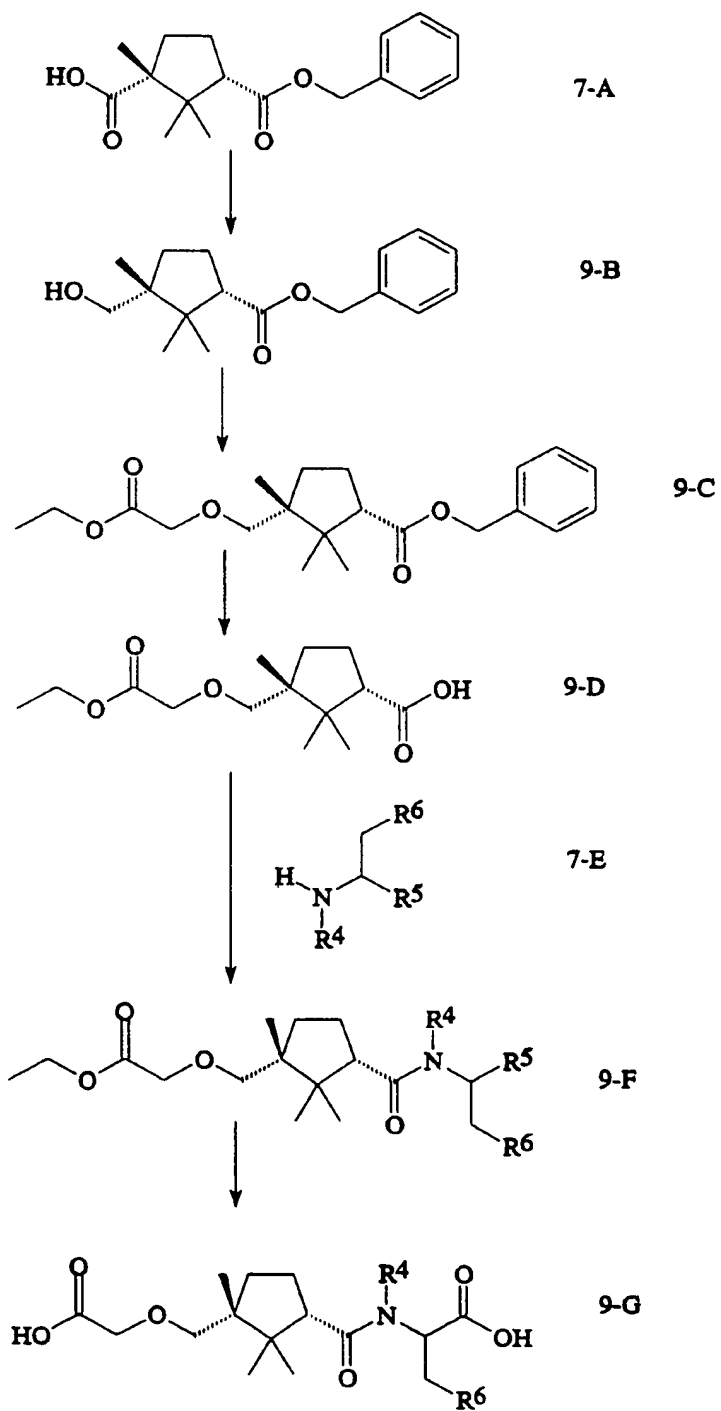
10 Scheme 8, 8-G: wherein R⁸⁻¹ = H, R⁸⁻² = H, R⁴ = H, R⁵ = CO₂H, R⁶ = 4-[(2,6-Dichlorophenyl)methoxy]phenyl
Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[(2-amino-2-oxoethyl)-amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine (Example 187) (C₂₈H₃₃Cl₂N₃O₆)
is prepared from 8-F (R⁸⁻¹ = H, R⁸⁻² = H, R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-[(2,6-dichlorophenyl)methoxy]phenyl) as
20 taught by Scheme 8.
¹H NMR(300MHz, DMSO-d₆) 7.74 (2H), 7.55-7.40 (4H), 7.15 (3H), 6.94 (3H), 5.16 (2H), 4.41 (1H), 3.75-3.48 (2H), 3.1-2.8 (2H), 2.63 (1H), 2.33 (1H), 1.87 (1H), 1.54 (1H), 1.32 (1H), 1.17 (3H), 1.08 (3H), 0.58 (3H); MS (FAB) m/z
25 (rel. intensity) 578 (M+H, 99), 581 (30), 580 (72), 579 (57), 578 (99), 577 (19), 504 (17), 322 (18), 239 (35), 161 (29), 159 (34); HRMS (FAB) m/z calcd for C₂₈H₃₃Cl₂N₃O₆ +H⁺ 578.1824, found 578.1836.

71

Scheme 9

Example 183



Preparation of Example 183

Scheme 9, 9-G: wherein R⁴ = H, R⁶ = 4-

[(2,6-dichlorobenzoyl)amino]phenyl

Stereochemistry = (1S-cis)-L

5 (1S-cis)-N-[[3-(carboxymethoxymethyl)-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (Example 183)
7-A (1.15 g, 3.96 mmol) was dissolved in dry THF (5 mL). The reaction flask was immersed in a -15 °C bath
10 (ethylene glycol/CO₂), then diborane-tetrahydrofuran (1M, 1 equiv, 3.96 mmol, 3.96 mL) was added slowly. The reaction solution was stirred at -15 °C under N₂ during the day, and was equilibrated to room temperature overnight. The reaction solution was
15 treated with potassium carbonate (1.2 g) in H₂O (25 mL). The THF layer was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with saturated NaCl (20 mL) and dried (MgSO₄). Solvent was removed in
20 vacuo from the mixture to yield 0.83 g (76%) of 9-B. The crude product was chromatographed, initially using CH₂Cl₂, as eluent followed by CH₂Cl₂/MeOH (5%). Recovered desired product 9-B (0.76 g, 69%) from column: ¹H NMR (CDCl₃) δ 0.80 (3 H), 1.00 (3 H), 1.11 (3 H), 1.32-1.47 (1 H), 1.62-1.91 (2 H), 2.09-2.22 (1H), 2.86 (1 H), 3.48-3.59 (2 H), 5.08-5.18 (2 H), 7.28-7.41 (5 H).

A solution of benzyl ester 9-B (0.76 g, 2.75 mmol) in CH₂Cl₂ (10 mL) was treated at 0 °C and under N₂ with
30 ethyl diazoacetate (5 equiv, 13.75 mmol, 1.4 mL) and a catalytic amount of HBF₄ (0.1 equiv, 0.03 mL). The reaction solution was stirred under N₂ overnight while the bath temperature equilibrated to room temperature. Solvent was removed under reduced
35 pressure to yield 1.8 g of product. Crude product was

subjected to silica gel (35 mm x 15.2 cm) flash column chromatography, eluting with 2%-10% EtOAc/hexanes, to provide 0.64 g (64%) of 9-C: ^1H NMR (CDCl_3) δ 0.81 (3H), 1.05 (3 H), 1.12 (3 H), 1.22-1.31 (3 H), 1.32-1.43 (1 H), 1.54-1.62 (2 H), 1.65-1.92 (2 H), 2.08-2.23 (1 H), 2.85 (1 H), 3.28 (1 H), 3.47 (1 H), 3.96-4.08 (2H), 4.14-4.25 (2 H), 5.07-5.18 (2H), 7.28-7.40 (5 H).

Benzyl ester 9-C (0.3 g, 0.83 mmol) was dissolved in absolute EtOH (10 mL). The solution was treated with a catalytic amount of 10% Pd/C (0.2 g) and hydrogenated at 20 psi for 1 h on a Parr hydrogenation apparatus. The suspension was filtered through a Celite cake and washed cake with EtOH. Solvent was removed from the filtrate under reduced pressure to yield 0.19 g (84%) of 9-D: ^1H NMR (CDCl_3) δ 0.90 (3 H), 1.06 (3 H), 1.16 (3 H), 1.19-1.32 (3 H), 1.33-1.45 (1H), 1.65-1.92 (2 H), 2.03-2.18 (1 H) 2.83 (1 H), 3.29 (1 H). 3.49 (1 H), 3.95-4.11 (2H), 4.19 (2 H).

Dissolved acid 9-D (0.18 g, 0.66 mmol), HOBt (1.2 equiv, 0.81 mmol, 0.11 g), DMAP (0.11 equiv, 0.074 mmol, 0.009 g), EDCI (1.2 equiv, 0.78 mmol, 0.15 g) and Et_3N (3.8 equiv, 2.5 mmol, 0.35 mL) in CH_2Cl_2 (10 mL) at 0°C. The reaction mixture was stirred for several minutes and then 7-E-1 (1.0 equiv, 0.69 mmol, 0.28 g) was added. The mixture was stirred overnight while the bath temperature equilibrated to room temperature. The reaction mixture was concentrated to dryness under reduced pressure. The residue was quenched with acidic H_2O (30 mL) and extracted with CHCl_3 (3 x 15 mL). The organic layers were combined, washed with saturated NaHCO_3 (30 mL), dried (MgSO_4) and solvent was removed under reduced pressure. Crude product was purified by silica gel (20 mm x 22.9 cm) flash chromatography using 90% CH_2Cl_2 /EtOAc as eluent.

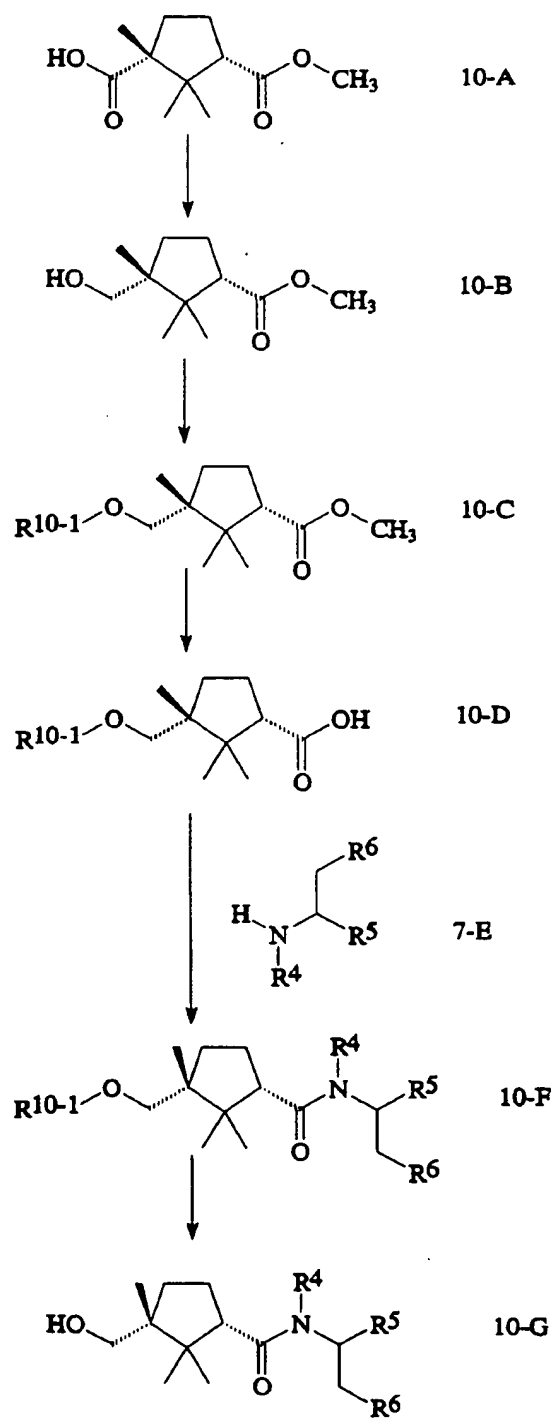
Fractions containing the compound were combined and solvent was removed under reduced pressure. The product was dissolved in $\text{CH}_3\text{CN}:\text{H}_2\text{O}$, frozen and lyophilized to yield 0.18 g (44%) of 9-F (where $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$ and $\text{R}^6 = \text{C}_6\text{H}_4\text{OCH}_2\text{C}_6\text{H}_3\text{Cl}_2$): ^1H NMR (CDCl_3) δ 0.82 (3 H), 1.05 (3 H), 1.12 (3 H), 1.27 (2 H), 1.31-1.43 (1 H), 1.59-1.84 (2 H), 2.05-2.21 (1 H), 2.55 (1 H), 3.03-3.23 (2 H), 3.30 (1 H), 3.47 (1 H), 3.74 (3 H), 3.93-4.09 (2 H), 4.19 (2 H), 4.90 (2 H), 5.76 (1 H), 7.11 (2 H), 7.24-7.39 (3 H), 7.47 (1 H), 7.57 (2 H); IR (mineral oil mull) 3292, 3193, 3123, 3064, 3033, 2951, 2922, 2870, 2855, 2854, 1748, 1657, 1656, 1606, 1579, 1562, 1537, 1515, 1461, 1431, 1414, 1376, 1348, 1324, 1271, 1207, 1196, 1153, 1129, 1023, 800, 781 cm^{-1} ; MS (FAB) for $\text{C}_{31}\text{H}_{38}\text{Cl}_2\text{N}_2\text{O}_7$, m/z (relative intensity) 623 ($[(\text{M} + \text{H})^+]$, 49), 622 ($[(\text{M} + \text{H})^+]$, 29), 621 ($[(\text{M} + \text{H})^+]$, 71), 620 (M^+ , 71), 517 (12), 351 (16), 349 (22), 175 (16), 173 (26), 151 (27), 123 (100). Anal. Calcd for $\text{C}_{31}\text{H}_{38}\text{Cl}_2\text{N}_2\text{O}_7$: C, 59.91; H, 6.16; N, 4.51; Cl, 11.41; Found: C, 59.67; H, 6.09; N, 4.63; Cl, 11.50. Corrected for 0.40% H_2O found by Karl Fischer analysis.

To a solution of methyl ester 9-F ($\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$, $\text{R}^6 = \text{C}_6\text{H}_4\text{OCH}_2\text{C}_6\text{H}_3\text{Cl}_2$) (0.11 g, 0.18 mmol) in MeOH (5 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (5 equiv, 0.88 mmol, 0.04 g) in H_2O (1 mL). The reaction solution was allowed to stir for about 2 hrs. The solvent was removed in vacuo. The residue was dissolved in H_2O (30 mL) and acidified with HCl. The resulting precipitate was filtered and washed with H_2O . The precipitate was dissolved in 50% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (10 mL), was frozen and lyophilized to yield 0.083 g (80%) of **Example 183** (9-G: where $\text{R}^4 = \text{H}$ and $\text{R}^6 = \text{C}_6\text{H}_4\text{OCH}_2\text{C}_6\text{H}_3\text{Cl}_2$): ^1H NMR (MeOD) δ 0.79 (3 H), 1.00 (3 H), 1.05 (3 H), 1.23-1.41 (1 H), 1.60-1.78 (2 H), 1.91-2.05 (1 H), 2.72 (1 H), 2.98 (1 H), 3.20 (1 H), 3.46 (1 H), 3.93-4.08 (2 H), 4.66-4.78 (1 H), 7.24 (2 H), 7.38-7.51 (3 H), 7.57 (2 H), 7.73 (1 H); IR

(mineral oil mull) 3270, 3193, 3123, 3056, 3034, 2954, 2928, 2854, 1731, 1657, 1607, 1562, 1537, 1516, 1461, 1459, 1432, 1414, 1376, 1326, 1272, 1220, 1195, 1126, 800, 781 cm^{-1} ; MS (FAB) for $\text{C}_{28}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_7$, m/z (relative intensity) 581 ($([\text{M} + \text{H}]^+, 51)$), 580 ($([\text{M} + \text{H}]^+, 29)$), 579 ($([\text{M} + \text{H}]^+, 76)$), 578 ($\text{M}^+, 8)$), 337 (12), 335 (18), 175 (19), 173 (29), 161 (18), 151 (18), 123 (100).
Anal. Calcd for $\text{C}_{28}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_7$: C, 58.04; H, 5.57; N, 4.84; Cl, 12.24; Found: C, 57.87; H, 5.44; N, 4.97; Cl, 12.29. Corrected for 2.17% H_2O found by Karl Fischer analysis.

Scheme 10

R^{10-1} is defined as methyl or CH_2-OCH_3 .



Preparation of Example 192:

Scheme 10, 10-G: wherein $R^4 = H$, $R^5 = CO_2H$,

$R^6 = 4-[(2,6\text{-dichlorophenyl})\text{methoxy}]\text{phenyl}$

Stereochemistry = (1*S*-cis)-L

5 (1*S*-cis)-O-[(2,6-Dichlorophenyl)methyl]-N-[(3-hydroxy-2,2,3-trimethylcyclopentyl)carbonyl]-L-tyrosine (Example 192).

Into a 100 mL oven dried round bottom flask was placed (1*S*-cis)-[3-carboxy-2,2,3trimethyl]cyclopentane
10 carboxylic acid methyl ester (10-A) (5.0 g, 23 mmol, 1 equiv), followed by dry THF (20 mL). The reaction flask was immersed in a -15°C bath (ethylene glycol/dry ice) and then boron
trifluoride-tetrahydrofuran (1 equiv, 1 M, 23 mmol, 23
15 mL) was slowly added. [Note: observed mild evolution of H₂ gas]. The reaction solution was allowed to stir for 24 hrs under N₂. The solution was stirred in the -15°C bath during the day, and the bath was permitted to reach room temperature overnight. Silica gel
20 Thin-layer chromatography, using 1:1 hexanes/ethyl acetate as eluent, showed that the starting material was consumed. Consequently, the reaction solution was quenched with H₂O (100 mL) and then treated with potassium carbonate (6 g). The THF phase was separated
25 while the aqueous phase was extracted with EtOAc (3 x 80 mL). The organic phases were combined, washed with saturated NaCl (100 mL) and dried (MgSO₄). The solvent was removed via rotary evaporator and then by overnight hi vacuum conditions to yield 4.7 g of crude
30 product. Crude product was subjected to a silica gel (35 mm x 25.4 cm) flash chromatography column. Elution with 5% EtOAc/hexanes yielded 4.0 g (87%) of 10-B as a clear oil: ¹H NMR (CDCl₃) δ 0.79 (3 H), 0.99 (3 H), 1.10 (3 H), 1.32-1.43 (1 H), 1.48 (H),
35 1.63-1.88 (2 H), 2.04-2.15 (1 H), 2.8 (1 H), 3.52 (2 H), 3.66 (3 H); IR (mineral oil mull) 3445, 2968,

2878, 1734, 1719, 1456, 1436, 1372, 1358, 1270, 1218, 1203, 1173, 1031, 1006 cm^{-1} ; MS (FAB) for $\text{C}_{11}\text{H}_{20}\text{O}_3$, m/z (relative intensity) 202 ($[\text{M} + 2\text{H}]^+$, 11), 201 ($[\text{M} + \text{H}]^+$, 100), 200 (M^+ , 0.9), 183 (11), 169 (8), 151 (8), 123 (29). Anal. for $\text{C}_{11}\text{H}_{20}\text{O}_3$: C, 65.97; H, 10.07; Found: C, 65.94; H, 9.91. Corrected for 0.85% H_2O found by Karl Fischer analysis.

(1S-cis)-[3-hydroxymethyl-2,2,3-trimethyl]-cyclopentane carboxylic acid methyl ester 10B (1.5 g, 7.5 mmol) was dissolved in CH_2Cl_2 (35 mL). Cooled flask to 0 °C, slowly added chloromethyl methyl ether (3.3 equiv, 25 mmol, 1.9 mL) and then added DIEA (5.87 mL, 4.5 equiv, 3.4 mmol). The bath temperature was allowed to equilibrate to room temperature while the reaction mixture was stirred for four days. Solvent was removed via a rotary evaporator. Crude product was dissolved in toluene, the insoluble precipitate was filtered and the concentrated filtrate was chromatographed on silica gel (35 mm x 5.2 cm) flash chromatography using 2% EtOAc/hexanes as eluent to yield 1.37 g (75%) of 10-C (where R^{10-1} = methoxymethyl): ^1H NMR (CDCl_3) δ 0.80 (3 H), 1.02 (3 H), 1.12 (3 H), 1.34-1.45 (1 H), 1.57 (H), 1.67-1.87 (2 H), 2.07-2.18 (1 H), 2.82 (1 H), 3.31 (1 H), 3.36 (3 H), 3.45 (1 H), 3.67 (3 H), 4.56-4.61 (2 H).

Compound 10-C (1.57 g, 6.4 mmol) was dissolved in THF (20 mL) and treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (10 equiv, 64 mmol, 2.7 g) in H_2O (30 mL), H_2O_2 (6 mL), H_2O (16 mL) and MeOH (16 mL). The mixture was refluxed overnight. The solvent was removed in vacuo, crude residue was quenched with H_2O (35 mL) and the pH was lowered to 5 with 10%, 6N or 12N hydrochloric acid. Extracted aqueous portion with EtOAc (3 x 20 mL) and then with CHCl_3 (3 x 20 mL). Organic layers were combined, dried (MgSO_4) and solvent removed on rotary evaporator.

Crude product was subjected to a silica gel (35 mm x 15.2 cm) flash chromatography column using 80% hexanes/EtOAc as eluent to yield 1.1 g (75%) of 10-D (where R^{10-1} = methoxy methyl): ^1H NMR (CDCl_3) δ 0.89 (3 H), 1.03 (3 H), 1.16 (3 H), 1.36-1.46, 1.68-1.89, 2.04-2.18 (1 H), 2.85 (1 H), 3.32 (1 H), 3.36 (3 H), 3.47 (1H), 4.57-4.62 (2 H).

Compound 10-D (0.83 g, 3.6 mmol), HOBT (1.13 equiv, 4.1 mmol, 0.55 g), DMAP (0.11 equiv, 0.4 mmol, 0.048 g), EDCI (1.1 equiv, 4.0 mmol, 0.76 g) and Et_3N (3.6 equiv, 13 mmol, 1.8 mL) were mixed in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred for several minutes, and then added O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester hydrochloride 7-E-2·HCl (wherein R^4 = H, R^5 = CO_2CH_3 , R^6 = 4-[(2,6-dichlorophenyl)methoxy]phenyl) (1 equiv, 3.6 mmol, 1.4 g). The mixture was stirred overnight while bath temperature equilibrated to room temperature. Reaction mixture was concentrated to dryness under reduced pressure. The residue was quenched with acidic H_2O (70 mL), and extracted with CHCl_3 (3 x 35 mL). Organic layers were combined, washed with saturated NaHCO_3 (40 mL), dried (MgSO_4) and solvent was removed under reduced pressure. Crude product was subjected to a silica gel (35 mm x 15.2 cm) flash chromatography column using 10% EtOAc/hexanes as eluent to yield 1.6 g (78%) of 10-F-1 (10-F (where R^{10-1} = methoxymethyl, R^4 = H, R^5 = CO_2CH_3 , and R^6 = 4-[(2,6-dichlorophenyl)methoxy]phenyl-): ^1H NMR (CDCl_3 , 400 MHz) δ 0.82 (3 H), 1.03 (3 H), 1.11 (3 H), 1.33-1.42 (1 H), 1.61 (2 H), 1.63-1.82 (2 H), 2.08-2.21 (1 H), 2.56 (1 H), 3.03-3.16 (2 H), 3.31 (1 H), 3.36 (3 H), 3.46 (1 H), 3.75 (3 H), 4.57-4.61 (2 H), 4.85-4.93 (1 H), 5.26 (2 H), 5.72 (1 H), 6.96 (2 H), 8.6 (2 H), 7.22-7.28 (1 H), 7.37 (2 H); IR (mineral oil mull) 2951, 2879, 1746, 1668, 1657, 1565, 1511, 1468, 1439,

1382, 1371, 1241, 1216, 1197, 1179, 1148, 1108, 1096, 1047, 1019, 780, 768 cm^{-1} ; MS (FAB) for $\text{C}_{29}\text{H}_{37}\text{Cl}_2\text{N}_1\text{O}_6$, m/z (relative intensity) 568 ($[\text{M} + \text{H}]^+$, 69), 566 ($[\text{M} + \text{H}]^+$, 100), 565 (M^+ , 12), 506 (41), 504 (61), 336 (41), 161 (40), 159 (62), 123 (83), 45 (53). Anal. Calcd for $\text{C}_{29}\text{H}_{37}\text{Cl}_2\text{N}_1\text{O}_6$: C, 61.48; H, 6.58; N, 2.47; Cl, 12.52; Found: C, 61.30; H, 6.55; N, 2.80; Cl, 12.57. Corrected for 0.11% H_2O found by Karl Fischer analysis.

Compound 10-F (0.74 g, 1.3 mmol) was dissolved in MeOH (30 mL) and treated with concentrated HCl (5 mL) and stirred at room temperature for 24 hrs. The solvent was removed in vacuo to yield a residue that was taken up in CHCl_3 and washed with saturated NaHCO_3 . [Note: upon treatment with saturated NaHCO_3 a precipitate formed which was filtered and washed with CHCl_3 .] Filtrate volume was reduced in vacuo and subjected to a silica gel (35 mm x 16.5 cm) flash chromatography column using 50% hexanes/EtOAc as eluent. Fractions containing pure compound were combined and solvent was removed under reduced pressure. The residue was dissolved in 50% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (10 mL), frozen and lyophilized to yield 0.23 g (34%) of 10-G (where $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$ and $\text{R}^6 = 4-[(2,6\text{-dichlorophenyl)methoxy}]$ phenyl-: ^1H NMR (CDCl_3 , 400 MHz) δ 0.84 (3 H), 1.00 (3 H), 1.10 (3 H), 1.37-1.48 (1 H), 1.69-1.82 (2 H), 2.09-2.21 (1 H), 2.55 (1 H), 3.02-3.18 (2 H), 3.51-3.59 (2 H), 3.75 (3 H), 4.84-4.91 (1 H), 5.26 (2 H), 5.75 (1 H), 6.96 (2 H), 7.05 (2 H), 7.22-7.29 (1 H), 7.37 (2 H); IR (mineral oil mull) 3428, 3322, 2923, 2870, 2854, 1743, 1654, 1565, 1511, 1466, 1439, 1377, 1298, 1278, 1240, 1197, 1179, 1018, 1003, 780, 768 cm^{-1} ; MS (FAB) for $\text{C}_{27}\text{H}_{33}\text{Cl}_2\text{N}_1\text{O}_5$, m/z (relative intensity) 524 ($[\text{M} + \text{H}]^+$, 65), 523 ($[\text{M} + \text{H}]^+$, 41), 522 ($[\text{M} + \text{H}]^+$, 100), 521 (M^+ , 19), 354 (21), 338 (21), 336 (29), 161 (21), 159 (34), 123 (38). Anal. Calcd for $\text{C}_{27}\text{H}_{33}\text{Cl}_2\text{N}_1\text{O}_5$: C, 62.07; H,

6.37; N, 2.68; Cl, 13.57; Found: C, 61.85; H, 6.27; N, 2.85; Cl, 13.50. Corrected for 0.44% H₂O found by Karl Fischer analysis.

Compound 10-G (0.19 g, 0.36 mmol) was dissolved in
5 CH₃OH (4 mL) and treated with LiOH.H₂O (10 equiv, 0.15 g, 3.6 mmol) in H₂O (4 mL). Additional MeOH (2 mL) was added to ensure solubility. The solution was stirred for 2 h at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in
10 warm H₂O (20 mL) (Note: room temperature H₂O caused aqueous solution to gel). The pH of the solution was lowered to 2 with 1.0 N HCl and the resulting precipitate was filtered, washed with H₂O and dried to yield 0.17 g (93%) of Example 192 (10-G: where R⁴ = H,
15 R⁵ = CO₂H and R⁶ = 4-[(2,6-dichlorophenyl)methoxy]phenyl-): unable to determine mp due to compound shrinkage at 80 °C; ¹H NMR (CDCl₃) δ 0.81 (3 H), 0.97 (3 H), 1.06 (3 H), 1.35-1.48 (1 H), 1.65-1.88 (2 H), 2.03-2.18 (1 H), 2.55 (1 H),
20 3.04-3.27 (2 H), 3.48-3.58 (2 H), 4.81-4.89 (1 H), 5.24 (2 H), 5.85 (1 H), 6.96 (2 H), 7.12 (2 H), 7.19-7.29 (1 H), 7.32-7.38 (2 H); IR (mineral oil mull) 3421, 3332, 3058, 3030, 2954, 2920, 2871, 2855, 1729, 1653, 1612, 1585, 1565, 1511, 1466, 1439, 1377,
25 1299, 1241, 1196, 1179, 1018, 1003, 779, 769 cm⁻¹; MS (FAB) for C₂₆H₃₁Cl₂N₁O₅; m/z (relative intensity) 510 ([M + H]⁺, 66), 509 ([M + H]⁺, 37), 508 ([M + H]⁺, 100), 507 (M⁺, 15), 340 (12), 324 (15), 322 (22), 161 (23), 159 (36), 123 (45). Anal. Calcd for C₂₆H₃₁Cl₂N₁O₅: C, 61.42; H, 6.15; N, 2.76; Cl, 13.95; Found: C, 61.33; H, 6.16;
30 N, 2.93; Cl, 13.74. Corrected for 1.61% H₂O found by Karl Fischer analysis.

Preparation of Example 198:

Scheme 10, 10-F = wherein R^{10-1} = methyl, R^4 = H, R^5 = CO_2H , R^6 = 4-[(2,6-dichlorophenyl)methoxy]phenyl

Stereochemistry = (1S-cis)-L

5 (1S-cis)-O-[(2,6-Dichlorophenyl)methyl]-N-[(3-methoxymethyl-2,2,3-trimethylcyclopentyl)carbonyl]-L-tyrosine (Example 198).

Alcohol 10-B (1.0 g, 4.8 mmol), in Et_2O (20 mL), was treated with boron trifluoride dimethyl etherate (0.1
10 equiv, 0.48 mmol, 0.06 mL) and an excess amount of $\text{CH}_2\text{N}_2/\text{Et}_2\text{O}$. The reaction mixture was stirred overnight. The mixture was filtered and solvent was removed on rotary evaporator. Crude product was subjected to a silica gel (35 mm x 16.5 cm) flash chromatography
15 column using 1% EtOAc /pentane as eluent to yield 0.69 g (67%) of 10C (where R^{10-1} = methyl): ^1H NMR (CDCl_3) δ 0.79 (3 H), 1.00 (3 H), 1.10 (3 H), 1.32-1.43 (1 H), 1.60-1.89 (2 H) 2.04-2.20 (1 H), 2.80 (1 H), 3.16 (1H), 3.28 (1 H), 3.31 (3 H), 3.68 (3 H).

20 Ester 10-C (0.37 g, 1.7 mmol) was dissolved in THF (40 mL) and treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (10 equiv, 17 mmol, 0.71 g) in H_2O (20 mL), MeOH (10 mL) and H_2O_2 (10 mL). The mixture was heated at reflux for about 8 h. Solvent was removed via a rotary evaporator.

25 Dissolved residue in H_2O (50 mL), lowered pH to 5 with hydrochloric acid, extracted aqueous portion with EtOAc (3 x 25 mL) followed by CHCl_3 (3 x 25 mL). Organic extracts were combined, dried (MgSO_4), and solvent was removed under reduced pressure to yield
30 0.44 g of 10-D (wherein R^{10-1} = Me): ^1H NMR (CDCl_3) δ 0.86 (3 H), 1.00 (3 H), 1.14 (3 H), 1.34-1.44 (1 H), 1.62-1.89 (2 H), 2.01-2.15 (1 H), 2.83 (1 H), 3.16 (1 H), 3.29 (1 H), 3.30 (3 H).

Compound 10-D (0.25 g, 1.2 mmol), HOBT (1.13 equiv,
35 1.41 mmol, 0.19 g), DMAP (0.11 equiv, 0.14 mmol, 0.017

g), EDC (1.1 equiv, 1.37 mmol, 0.25 g) and Et₃N (3.6 equiv, 4.49 mmol, 0.6 mL) were mixed in CH₂Cl₂ (10 mL) at 0 °C. Stirred the reaction mixture for several minutes then added 7-E-2·HCl (0.8 equiv, 1.0 mmol, 0.4 g). The mixture was stirred overnight while the bath temperature equilibrated to room temperature. Concentrated reaction mixture to dryness under reduced pressure. Residue was treated with acidic H₂O (30 mL) and extracted with CHCl₃ (3 x 15 mL). Combined organic layers, washed with saturated NaHCO₃ (20 mL), dried (MgSO₄) and solvent was removed under reduced pressure. Crude product was purified by silica gel (20 mm x 16.5 cm) flash chromatography using 10%-15% EtOAc/hexanes as eluent. Fractions containing the compound were combined and solvent was removed under reduced pressure. The residue was dissolved in 50% CH₂CN:H₂O (50 mL), frozen and lyophilized to yield 0.24 g (45%) of 10-F (where R¹⁰⁻¹ = methyl, R⁴ = H, R⁵ = CO₂CH₃, and R⁶ = 4-[(2,6-dichlorophenyl)methoxy]phenyl-): ¹H NMR (CDCl₃) δ 0.79 (3 H), 0.99 (3 H), 1.09 (3 H), 1.32-1.43 (1 H), 1.61 (2 H), 1.65-1.85 (2 H), 2.08-2.23 (1 H), 2.53 (1 H), 3.01-3.18 (2 H), 3.16 (1 H), 3.28 (1 H), 3.30 (3H), 3.74 (3 H), 4.83-4.91 (1 H), 5.25 (2 H), 5.74 (1 H), 6.96 (2 H), 7.05 (2 H), 7.23-7.29 (1 H), 7.35-7.40 (2 H): IR (mineral oil mull) 3317, 2956, 2924, 2871, 2857, 2855, 1745, 1652, 1612, 1565, 1511, 1466, 1439, 1378, 1298, 1278, 1240, 1197, 1178, 1106, 1096, 1017, 1000, 779, 768 cm⁻¹; MS (FAB) for C₂₈H₃₅Cl₂N₁O₅, m/z (relative intensity) 538 ([M + H]⁺, 65), 537 ([M + H]⁺, 40), 536 ([M + H]⁺, 100), 535 (M⁺, 16), 338 (16), 336 (24), 161 (18), 159 (28), 123 (69). Anal. Calcd for C₂₈H₃₅Cl₂N₁O₅·nH₂O: C, 62.69; H, 6.58; N, 2.61; Cl, 13.22; Found: C, 62.44; H, 6.35; N, 2.88; Cl, 13.11. Corrected for 0.37% H₂O found by Karl Fischer analysis.

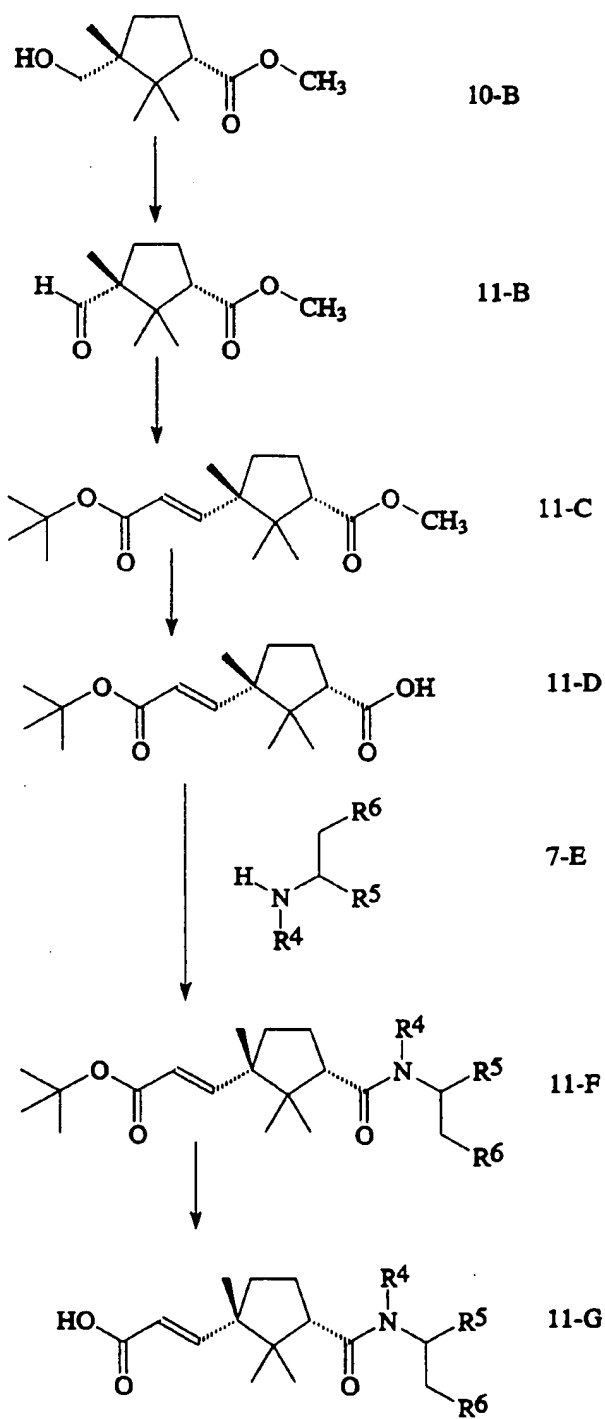
Ester 10-F (0.27 g, 0.5 mmol) was treated with LiOH·H₂O (10 equiv, 5.0 mmol, 0.21 g) in H₂O (8 mL). The reaction mixture was stirred for 1 h. THF (3 mL) was added to complete dissolution of starting material and MeOH (3 mL) was added to convert reaction mixture to homogeneous solution. The volume was reduced under vacuum. H₂O (40 mL) was added and the mixture was acidified with HCl. The resulting precipitate was filtered, washed with H₂O, and dried under house vacuum to yield 0.26 g (99%) of **Example 198** (10-F: where R¹⁰⁻¹ = methyl; R⁴ = H; R⁵ = CO₂H and R⁶ = 4-[(2,6-dichlorophenyl)methoxy]phenyl- stereochemistry = (1S-cis)-L): ¹H NMR (CDCl₃) δ 0.77 (3 H), 0.98 (3 H), 1.05 (3 H), 1.31-1.42 (1 H), 1.61-1.85 (2 H), 2.01-2.16 (1 H), 2.53 (1 H), 3.07-3.28 (2 H), 3.15 (1 H), 3.27 (1 H), 3.29 (3 H), 4.79-4.87 (1 H), 5.24 (2 H), 5.77 (1 H), 6.97 (2 H), 7.12 (2 H), 7.21-7.29 (1 H), 7.32-7.39 (2 H); IR (mineral oil mull) 3424, 3335, 3032, 2955, 2924, 2855, 1734, 1644, 1612, 1586, 1565, 1512, 1466, 1439, 1377, 1299, 1241, 1197, 1179, 1107, 1096, 1018, 873, 779, 769 cm⁻¹; MS (FAB) for C₂₇H₃₃Cl₂N₁O₅, m/z (relative intensity) 524 ([M + H]⁺, 62), 523 ([M + H]⁺, 36), 522 ([M + H]⁺, 96), 521 (M⁺, 13), 324 (14), 322 (22), 161 (31), 159 (42), 123 (100). Anal. Calcd for C₂₇H₃₃Cl₂N₁O₅·nH₂O: C, 62.07; H, 6.37; N, 2.68; Cl, 13.57; Found: C, 62.04; H, 6.24; N, 2.90; Cl, 13.91. Corrected for 2.18% H₂O found by Karl Fischer analysis.

Preparation of Example 203:

Scheme 10, 10-F; where R¹⁰⁻¹ = methoxymethyl; R⁴ = H; R⁵ = CO₂H and R⁶ = 4-[(2,6-Dichlorophenyl)methoxy]phenyl-, Stereochemistry = (1S-cis)-L (1S-cis)-O-[(2,6-Dichlorophenyl)methyl]-N-[(3-methoxymethoxymethyl-2,2,3-trimethylcyclopentyl)carbonyl]-L-tyrosine (**Example 203**)

Compound 10-F-1 (10-F: (where R¹⁰⁻¹ = methoxymethyl, R⁴ = H, R⁵ = CO₂CH₃ and R⁶ = 4-[(2,6-

dichlorophenyl)methoxy]phenyl-) (0.25 g, 0.44 mmol) was dissolved in MeOH (3 mL). Treated the reaction solution with LiOH.H₂O (10 equiv, 4.4 mmol, 0.18 g) in H₂O (5 mL). Additional MeOH (2 mL) was added to ensure
5 solubility. [Note: reaction mixture turned clear within 1 hour of reaction time]. Solution was allowed to stir overnight at room temperature under N₂. Solvent volume was reduced on a rotary evaporator, the remaining material was diluted with H₂O (10 mL) and
10 acidified with hydrochloric acid. The resulting precipitate was filtered, washed with H₂O and dried under house vacuum to yield 0.23 g (95%) of Example 203. mp: unable to determine due to compound shrinkage at 60 °C; ¹H NMR (CDCl₃) δ 0.79 (3 H), 1.01
15 (3 H), 1.07 (3 H), 1.32-1.46 (1 H), 1.62-1.84 (2 H), 2.01-2.18 (1 H), 2.55 (1 H), 3.02-3.24 (2 H), 3.30 (1 H), 3.35 (3 H), 3.45 (1 H), 4.55-4.61 (2 H), 4.81-4.89 (1 H), 5.24 (2 H), 5.76 (1 H), 6.97 (2 H), 7.12 (2 H), 7.18-7.27 (1 H), 7.31-7.37 (2 H); IR (mineral oil
20 mull) 2930, 2872, 2855, 1736, 1638, 1612, 1511, 1466, 1439, 1377, 1241, 1196, 1179, 1147, 1108, 1045, 1020 cm⁻¹; MS (FAB) for C₂₈H₃₅Cl₂N₁O₆nH₂O, m/z (relative intensity) 554 ([M + H]⁺, 67), 552 ([M + H]⁺, 100), 551 (M⁺, 16), 492 (38), 490 (56), 322 (33), 161 (40),
25 159 (64), 123 (73), 45 (61). Anal. Calcd for C₂₈H₃₅Cl₂N₁O₆: C, 60.87; H, 6.39; N, 2.54; Cl, 12.83; Found: C, 60.73; H, 6.41; N, 2.69; Cl, 12.86. Corrected for 0.11% H₂O found by Karl Fischer analysis.

Scheme 11

Preparation 11-B

Scheme 11, 11-B

Stereochemistry = 1*S*-cis(1*S*-cis) 3-Formyl-2,2,3-

5 trimethylcyclopentanecarboxylic acid methyl ester
(11-B) (C₁₁H₂₀O₃)

To a solution of 10-B (2.57g, 12.8 mmol) in methylene
chloride (50 mL) is added a mixture of pyridinium
chlorochromate (3.05g, 14.15 mmol), magnesium sulfate
10 (4g, 33 mmol), and Celite. After overnight stirring,
the mixture is eluted through a short column of silica
gel (80g) using methylene chloride (500 mL) as the
eluant. Evaporation in vacuo gives 11-B as a
colorless liquid (2.09g, 82% yield).
15 ¹H NMR(CDCl₃) δ 9.65(1H), 3.67(3H), 2.81(1H),
2.40(1H), 2.23 (1H), 1.94(1H), 1.42(1H), 1.16(3H),
1.05 (3H), 0.88 (3H).

Preparation 11-C

Scheme 11, 11-C

20 Stereochemistry = 1*S*-cis, (*E*)

(1*S*-cis)-3-[2-[(1,1-dimethylethoxy)carbonyl]ethenyl]-
2,2,3-trimethylcyclopentanecarboxylic acid methyl
ester (11-C) (C₁₇H₂₈O₄)

To a dry N₂ flushed 100 mL flask is added t-butyl
25 diethyl phosphonoacetate (5 mL, 21.3 mmol) and THF
(dry, 20 mL). The flask is immersed in an ice water
bath and, five minutes later, NaH/oil (60% NaH, 0.5g,
12.5mmol) is added in portions. After thirty minutes,
11-B (2.08g, 10.5 mmol) is mixed with THF (dry, 15 mL)
30 and added via syringe over a five minute period.
Four hours later, the still cold solution is diluted
with toluene (200 mL), shaken with ice water (4 X 100
mL), and the organic layer evaporated to dryness in
vacuo, giving a colorless oil which is chromatographed

on silica gel (80 g) using a gradient from 0 to 4% ethylacetate/ hexane. A colorless oil 11-C is obtained (1.99g, 63% yield).

¹H NMR(CDCl₃) δ 6.92(1H), 5.68 (1H), 3.67 (3H), 2.84 (1H), 2.23 (1H), 1.99 (1H), 1.90 (1H), 1.49 (1H), 1.48 (9H), 1.06 (3H), 1.01 (3H), 0.71 (3H); IR (nujol) 1728, 1712, 1651, 1438, 1358, 1316, 1288, 1270, 1228, 1220, 1191, 1171, 1151, 1132, 1001cm⁻¹; MS (FAB) m/z (rel. intensity) 297 (M+H, 44), 297 (44), 242 (12), 241 (87), 224 (14), 223 (99), 195 (14), 191 (14), 135 (12), 57 (34), 41 (12); HRMS (FAB) calcd for C₁₇H₂₈O₄ +H⁺ 297.2065, found 297.2067; Anal. Calcd for C₁₇H₂₈O₄ : C, 68.89; H, 9.52; N; Found: C, 69.03; H, 9.18.

Preparation 11-D

Scheme 11, 11-D
Stereochemistry = 1*S*-cis, (*E*)

(1*S*-cis)-3-[2-[(1,1-dimethylethoxy)carbonyl]ethenyl]-2,2,3-trimethylcyclopentanecarboxylic acid (11-D)
(C₁₆H₂₆O₄)

A solution of LiOH·H₂O (0.65g, 15.4mmol) in H₂O (15mL) and aqueous H₂O₂ (5mL, 30%) is added to a solution of 11-C (1.52g, 5.13mmol) in methanol (30mL). After stirring for two days, the mixture is diluted with water (100mL) and evaporated in vacuo until all of the methanol is gone. The aqueous remainder is then shaken with diethyl ether (3X40mL) and then cooled in an ice water bath and brought to pH 5 using 1N aq. HCl. The resultant white precipitate 11-D is isolated by suction filtration (0.385g, 26% yield)

¹H NMR(CDCl₃): δ 6.94(1H), 5.69(1H), 2.88(1H), 2.27-1.84(3H), 1.53(1H), 1.49(9H), 1.11(3H), 1.02(3H), 0.81(3H); IR (nujol) 2729, 2669, 1707, 1647, 1418, 1393, 1316, 1305, 1242, 1154, 999, 976, 960, 944, 856cm⁻¹; MS (FAB) m/z (rel. intensity) 283 (M+H, 34), 566 (13), 283 (34), 228 (13), 227 (99), 210 (13), 209

(96), 191 (14), 181 (14), 57 (51), 41 (16); Anal.
 Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28; Found: C,
 67.84; H, 9.10.

Preparation 11-F-1

5 Scheme 11, 11-F: wherein $R^4 = H$, $R^5 = CO_2CH_3$,
 $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$
 Stereochemistry = [1S-[1 α ,3 α (E)]]-L

[1S-[1 α ,3 α (E)]]-N-[[3-[2-[(1,1-
 dimethylethoxy)carbonyl]ethenyl]-2,2,3-
 10 trimethylcyclopentyl]carbonyl]-4-[(2,6-
 dichlorobenzoyl)amino]-L-phenylalanine methyl ester
 (11-F-1) ($C_{33}H_{38}Cl_2N_2O_6$)
 A solution of 11-D (0.45g, 1.59mmol) in methylene
 chloride (15mL) is cooled in an ice water bath. To
 15 this stirred solution were added N,N-diisopropylethyl
 amine (2mL, 11.48mmol), EDC (0.335g, 1.75mmol), HOBT
 (0.25g, 1.85mmol), and 4-N,N-dimethylaminopyridine
 (0.02g, 0.16mmol), followed thirty minutes later by
 the 4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine
 20 methyl ester hydrochloride 7-E-1·HCl (7-E: $R^4 = H$, $R^5 =$
 CO_2CH_3 , $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl$)
 (0.67g, 1.66mmol). After two days, the reaction
 mixture is evaporated to dryness, mixed with toluene
 (200mL), and shaken with cold 0.5N aq. HCl (50mL)
 25 followed by water (4X50mL). The organic layer is then
 evaporated to dryness in vacuo to give an off-white
 solid which is recrystallized from ethyl acetate to
 give a white solid (11-F-1) (0.59g, 58% yield).
 1H NMR($CDCl_3$) δ 7.84(1H), 7.56(2H), 7.35-7.25(3H),
 30 7.08(2H), 6.90(1H), 5.77(1H), 5.65(1H), 4.87(1H),
 3.73(3H), 3.12(2H), 2.59(1H), 2.21(1H), 2.05(1H),
 1.85(1H), 1.49(1H), 1.47(9H), 1.03(3H), 0.99(3H),
 0.69(3H); MS(ES+) m/z 631.

Preparation 11-G-1

Scheme 11, 11-G: wherein $R^4 = H$, $R^5 = CO_2CH_3$,
 $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl$
 Stereochemistry = $[1S-[1\alpha,3\alpha(E)]]$

5 $[1S-[1\alpha,3\alpha(E)]]-N-[[3-(2-Carboxyethenyl)-2,2,3-$
 trimethylcyclopentyl]carbonyl]-4-[(2,6-
 dichlorobenzoyl)amino]-L-phenylalanine methyl ester
 (11-G-1) ($C_{29}H_{30}Cl_2N_2O_6$)

A solution of 11-F-1 (0.5g, 0.8mmol) in
 10 trifluoroacetic acid (3mL) is stirred overnight under
 nitrogen. The solution is then evaporated to dryness
 in vacuo, diluted with toluene (50mL) and evaporated
 to dryness again, giving 11-G-1 as an oil (0.45g, 97%
 yield).

15 1H NMR (300MHz, DMSO- d_6) 10.75(1H), 10.60(1H),
 7.96(1H), 7.64-7.44(4H), 7.23-7.14(3H), 6.88(1H),
 5.63(1H), 4.9(1H), 4.8(1H), 4.50(1H), 3.58(3H),
 3.03-2.70(2H), 2.50(1H), 2.1-1.2(4H), 0.92(3H),
 0.83(3H), 0.55(3H).

20 **Preparation of Example 182**

Scheme 11, 11-G: wherein $R^4 = H$, $R^5 = CO_2H$
 $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl$
 Stereochemistry = $[1S-[1\alpha,3\alpha(E)]]$

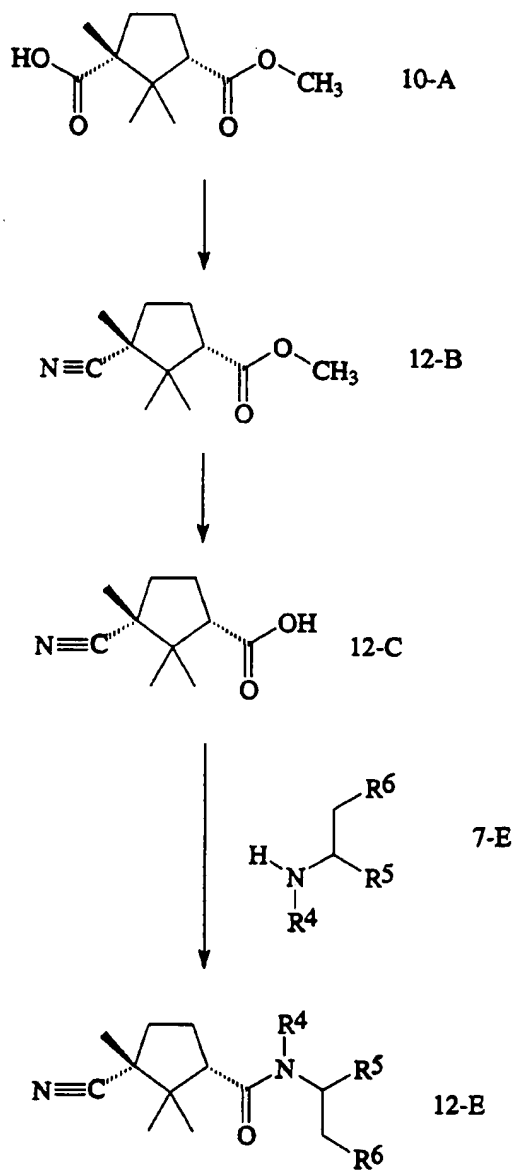
$[1S-[1\alpha,3\alpha(E)]]-N-[[3-(2-Carboxyethenyl)-2,2,3-$
 25 trimethylcyclopentyl]carbonyl]-4-[(2,6-
 dichlorobenzoyl)amino]-L-phenylalanine disodium salt
 (Example 182) ($C_{28}H_{28}Cl_2Na_2N_2O_6$)

To a solution 11-G-1 (0.45g, .78mmol) in methanol (5
 mL), in a flask cooled in an ice water bath, is added
 30 a solution of LiOH \cdot H $_2$ O (0.127g, 3mmol) in H $_2$ O (5mL).
 After two days, the mixture is diluted with water
 (50mL), evaporated in vacuo until the methanol is gone
 and then cooled to -10°C and brought to pH 2 using 1N
 aq. HCl. The resultant white precipitate is isolated

by suction filtration to give a white solid which is stirred with saturated aqueous NaHCO_3 (2mL) and then transferred to a C-18 reversed phase HPLC column and eluted with a gradient from 0.01%aq NaHCO_3 to 10%acetonitrile/0.01%aq NaHCO_3 . Evaporation is accomplished in vacuo to give ~~Example~~ 182 as a white solid (0.25 g, 51% yield).

^1H NMR(300MHz, DMSO- d_6) δ 7.51-7.42(5H), 7.06(2H), 6.39(1H), 5.49(1H), 4.10(1H), 2.99(1H), 2.86(1H), 2.56(1H), 1.85(2H), 1.61(1H), 1.29(1H), 0.90(3H), 0.85(3H), 0.51(3H); IR (nujol) 3393, 3257, 3124, 3035, 1654, 1604, 1562, 1544, 1515, 1431, 1398, 1325, 799, 778, 722 cm^{-1} ; MS (FAB) m/z (rel. intensity) 605 (M+H, 44), 629 (9), 627 (14), 608 (8), 607 (30), 606 (14), 605 (44), 585 (14), 583 (21), 73 (45), 23 (99); KF Water: 7.09%.

Scheme 12



Preparation of Example 184

Scheme 12, 12-E: wherein $R^4 = H$, $R^5 = CO_2H$, $R^6 =$

4-[(2,6-Dichlorobenzoyl)amino]phenyl

Stereochemistry = (1*S*-cis)-L

- 5 (1*S*-cis)-N-[[3-Cyano-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine.
Ester 10-A (5.0 g, 23.3 mmol) was dissolved in dry pyridine (100 mL). At 0°C, the reaction solution was
10 treated with methanesulfonyl chloride (MsCl) (1 equiv, 23.3 mmol, 1.8 mL). The mixture was stirred for two days, while the bath temperature equilibrated to room temperature. The reaction mixture was saturated with ammonia (NH₃) gas. Excess NH₃ was removed via a rotary
15 evaporator. The reaction mixture was treated with MsCl (10 equiv, 18 mL, 0.23 mol) and allowed to stir overnight. Solvent was removed under reduced pressure and resulting crude material was purified by a silica gel (35 mm x 15.2 cm) flash column chromatography
20 using 90% hexanes:EtOAc as eluent to yield 3.5 g of 12-B: ¹H NMR (CDCl₃) δ 1.08 (3 H), 1.19 (3 H), 1.32 (3 H), 1.73-2.01 (2 H), 2.25-2.41 (2 H), 2.71 (1 H), 3.70 (3 H).
Ester 12-B (0.7 g, 3.6 mmol) was dissolved in THF (20
25 mL) and treated with LiOH·H₂O (10 equiv, 1.5 g, 35.8 mmol) in H₂O (20 mL) and MeOH (10 mL). After 2 h, the solvent was removed in vacuo. The residue was dissolved in acidic H₂O (50 mL), for example 1N HCl, 10% H₂SO₄, or 1N AcOH, and was extracted with CHCl₃ (3 x
30 20 mL) to yield, upon usual work-up, 0.6 g (92%) of 12-C: ¹H NMR (CDCl₃) δ 1.17 (3 H), 1.25 (3 H), 1.34 (3H), 1.77-2.00 (2 H), 2.19-2.41 (2 H), 2.69-2.81 (1H).
Acid 12-C (0.6 g, 3.3 mmol), HOBT (1.13 equiv, 0.5 g),
35 DMAP (0.11 equiv, 0.04 g), EDC (1.1 equiv, 0.7 g),

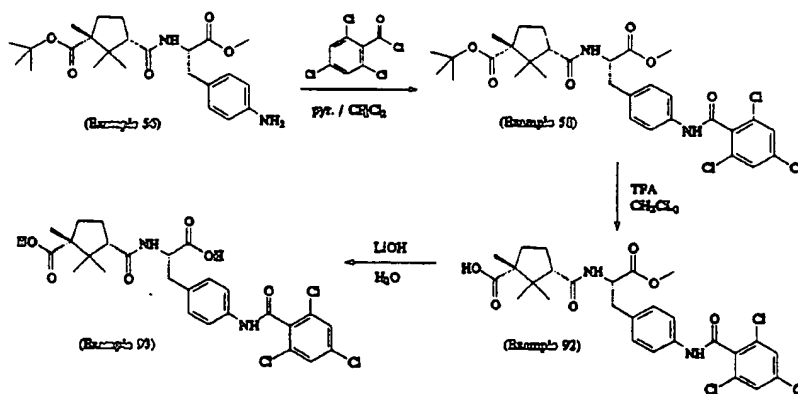
Et₃N (3.6 equiv, 1.6 mL) and CH₂Cl₂ (20 mL) were combined and the reaction was stirred for a couple of minutes. Then 7-E-1·HCl (0.75 equiv, 1.0 g) was added and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was triturated with THF. The precipitate was filtered, dissolved in a mixture of CH₃CN:H₂O, frozen and lyophilized to yield 12-E (where R⁴ = H, R⁵ = CO₂CH₃ and R⁶ = 4-[(2,6-dichlorobenzoyl)amino]phenyl): mp 170-174 °C; ¹H NMR (MeOD) δ 1.01 (3 H), 1.17 (3 H), 1.32 (3 H), 1.72-1.87 (2 H), 2.02-2.32 (2 H), 2.67 (1H), 2.97 (1H), 3.18 (1H), 3.71 (3 H), 4.73 (1H), 7.22 (2H), 7.38-7.50 (3H), 7.59 (2H); IR (mineral oil mull) 3282, 3252, 3314, 3192, 3125, 3075, 2954, 2925, 2870, 2855, 2235, 1750, 1738, 1653, 1610, 1562, 1541, 1516, 1458, 1431, 1415, 1379, 1332, 1274, 1260, 1243, 1231, 1214, 1195, 799 cm⁻¹; MS (FAB) for C₂₇H₂₉Cl₂N₃O₄, m/z (relative intensity) 532 ([M + H]⁺, 68), 531 ([M + H]⁺, 35), 530 ([M + H]⁺, 100), 529 (M⁺, 7), 351 (26), 349 (40), 175 (21), 173 (33), 136 (35), 109 (20). Anal. Calcd for C₂₇H₂₉Cl₂N₃O₄·nH₂O: C, 61.14; H, 5.51; N, 7.92; Cl, 13.37; Found: C, 61.32; H, 5.53; N, 7.94; Cl, 13.04. Corrected for 0.66% H₂O found by Karl Fischer analysis.

To a solution of the obtained 12-E (1.0 g, 1.9 mmol), in MeOH (25 mL) was added LiOH·H₂O (5 equiv, 9.4 mmol, 0.4 g) in H₂O (10 mL). The reaction solution was allowed to stir for 4 h. The reaction solution was reduced in vacuo to dryness. The residue was treated with n acidic H₂O (25 mL). The resulting precipitate was filtered and subjected to silica gel (35 mm x 15.2 cm) flash chromatography column using CH₃CN spiked with 0.1% acetic acid as an eluent. Fractions containing compound were combined and solvent was removed under reduced pressure. The residue was then dissolved in CH₃CN:H₂O, frozen and lyophilized to yield 0.62 g (63%)

of Example 184 (12-E: where $R^4 = H$, $R^5 = CO_2H$ and $R^6 = 4-[(2,6-dichlorobenzoyl)amino]phenyl$): mp: unable to determine due to compound shrinkage at 50 °C; 1H NMR (MeOD) δ 1.02 (3 H), 1.18 (3 H), 1.31 (3 H), 1.72-1.87 (2 H), 2.01-2.33 (2 H), 2.69 (1 H), 2.97 (1 H), 3.23 (1 H), 4.68-4.78 (1 H), 7.24 (2 H), 7.38-7.49 (3 H), 7.58 (2 H), 7.96 (1 H); IR (mineral oil mull) 3338, 3291, 3260, 3200, 3132, 3079, 3039, 2954, 2914, 2854, 2253, 1746, 1672, 1657, 1611, 1579, 1560, 1544, 1516, 1466, 1457, 1431, 1416, 1397, 1379, 1328, 1282, 1271, 1222, 1210, 1196, 1125, 812, 782, 800 cm^{-1} ; MS (FAB) for $C_{26}H_{27}Cl_2N_3O_4$, m/z (relative intensity) 518 ($[M + H]^+$, 68), 517 ($[M + H]^+$, 35), 516 ($[M + H]^+$, 100), 515 (M^+ , 7), 337 (16), 335 (24), 175 (18), 173 (27), 136 (23), 109 (12). Anal. Calcd for $C_{26}H_{27}Cl_2N_3O_4 \cdot nH_2O$: C, 60.47; H, 5.27; N, 8.14; Cl, 13.73; Found: C, 60.33; H, 5.25; N, 8.03; Cl, 13.62. Corrected for 4.58% H_2O found by Karl Fischer analysis

Scheme 13

Examples 58, 92 and 93



The Intermediate amine according to Example 56 (619 mg, 1.43 mmol) was dissolved in CH_2Cl_2 (5 mL) containing pyridine (0.3 mL, 3.58 mmol). To this

solution 2,4,6-trichlorobenzoyl chloride (246 mg, 1.58 mmol) was added and the solution stirred at RT for 6 h. The reaction was acidified with 1 N HCl (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined
5 organics were dried (Na₂SO₄), filtered, and the solvent removed in vacuo. The residue was chromatographed (SiO₂, gradient elution: 100% hexanes -> 50% EtOAc / hexanes) to provide Example 58 (866 mg, 95 %) as a colorless foam: ¹H NMR (300 MHz, CDCl₃), δ 7.56 (2H),
10 7.33 (2H), 7.08 (2H), 5.84 (1H), 4.8-4.9 (1H), 3.74 (3H), 3.0-3.2 (3H), 2.4-2.6 (2H), 2.0-2.2 (1H), 1.6-1.8 (1H), 1.43 (9H), 1.21 (3H), 1.14 (3H), 0.76 (3H);
¹³C NMR (75 MHz, CDCl₃), δ 174.92, 172.55, 172.00, 161.81, 136.29, 135.91, 134.46, 133.00, 132.69,
15 129.75, 128.08, 120.51, 80.19, 56.60, 54.33, 53.04, 52.35, 46.32, 37.14, 32.26, 27.99, 22.90, 22.39, 21.90, 20.50; ESMS (m/z) 639 (MH⁺).

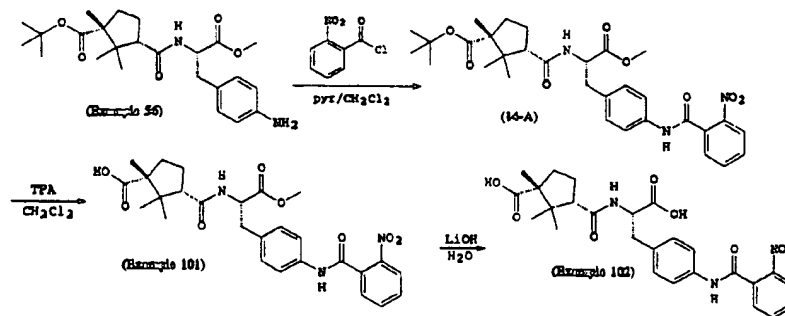
Example 58 (810 mg, 1.27 mmol) was dissolved in CH₂Cl₂ (5mL) containing TFA (5 mL). This reaction mixture
20 was stirred for 6 h at RT. Evaporation of the solvent under reduced pressure provided a crude oil. The residue was chromatographed (SiO₂, gradient elution: 100% hexanes -> 50% EtOAc/hexanes) to provide Example 92 (703 mg, 95 %) as a colorless foam: ¹H NMR (300
25 MHz, Acetone-d₆), δ 9.68 (1H), 7.66 (2H), 7.44 (2H), 7.17 (2H), 6.93 (1H), 4.88 (1H), 3.72 (3H), 3.17 (1H), 3.05 (1H), 2.79 (1H), 2.5-2.6 (1H), 2.1-2.2 (1H), 1.7-1.8 (1H), 1.4-1.5 (1H), 1.25 (3H), 1.21 (3H), 0.84 (3H); ¹³C NMR (75 MHz, Acetone-d₆), δ 176.92, 172.14,
30 171.14, 160.87, 136.16, 134.58, 134.48, 132.16, 132.12, 128.93, 127.08, 119.23, 59.24, 55.25, 52.60, 51.06, 45.64, 36.03, 31.71, 21.92, 21.63, 20.83, 20.06; ESMS (m/z) 583 (MH⁺).

Example 92 (684 mg, 1.17 mmol) was dissolved in H₂O
35 (8mL) containing LiOH (127 mg, 5.27 mmol). After 6 h

at RT the mixture was acidified with 3 N HCl (3 mL) and the precipitate filtered and washed with cold H₂O (3 mL). Drying under high vacuum provided Example 93 (547 mg, 82 %) as a colorless solid: ¹H NMR (300 MHz, Acetone-d₆), δ 9.96 (1H), 7.70 (2H), 7.58 (2H), 7.30 (2H), 4.8-4.9 (1H), 3.23 (1H), 3.07 (1H), 2.89 (1H), 2.5-2.6 (1H), 2.0-2.2 (1H), 1.6-1.7 (1H), 1.4-1.5 (1H), 1.26 (3H), 1.19 (3H), 0.81 (3H); ¹³C NMR (75 MHz, Acetone-d₆), δ 178.52, 174.10, 173.62, 162.22, 138.12, 136.08, 134.47, 133.69, 130.77, 128.90, 120.54, 56.92, 54.56, 53.89, 47.24, 37.48, 33.37, 23.52, 23.04, 22.31, 21.73; ESMS (m/z) 569 ([M-H]⁻).

Scheme 14

Examples 101 and 102.



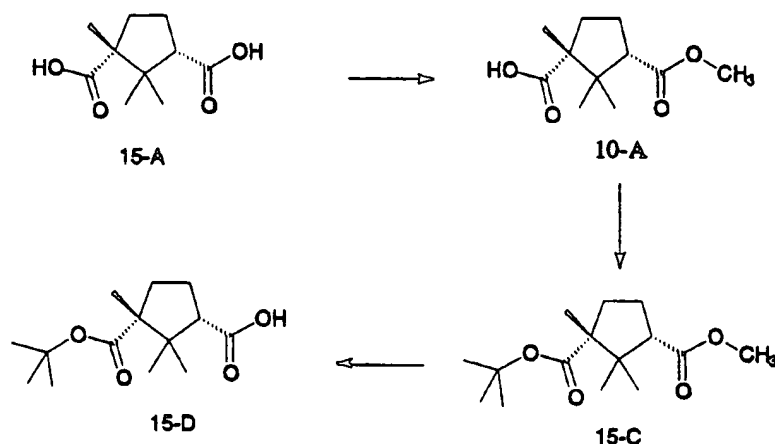
The compound according to Example 56 (810mg, 1.87mmol) was dissolved in Pyr/CH₂Cl₂ (5mL of each) and O-nitrobenzoyl chloride (383mg, 2.06mmol) was added under dry N₂. The reaction was stirred for 4 hours at RT. The solvent was evaporated under high vacuum and 1N HCl (20mL) was added to the residue. This was extracted with CH₂Cl₂ (3 x 25mL) and the combined organic phases were dried over Na₂SO₄. The solution was filtered, solvent evaporated and the residue chromatographed (SiO₂, gradient elution: 100% hexanes -> 50% EtOAc/hexanes) to provide the intermediate

(14-A) (808mg, 74%): ¹H NMR (300 MHz, CDCl₃), δ 8.4-8.6 (1H), 8.03 (1H), 7.6-7.7 (3H), 7.49 (2H), 7.04 (2H), 5.86 (1H), 4.7-4.8 (1H), 3.71 (3H), 3.0-3.2 (2H), 2.4-2.6 (2H), 2.0-2.1 (1H), 1.6-1.7 (1H), 1.4-1.5 (1H), 1.42 (9H), 1.20 (3H), 1.12 (3H), 0.73 (3H); ¹³C NMR (75 MHz, CDCl₃), δ 174.94, 172.61, 171.97, 164.57, 146.15, 136.64, 133.77, 132.76, 132.38, 130.56, 129.62, 128.63, 124.47, 120.56, 80.16, 56.58, 54.23, 53.05, 52.28, 46.31, 37.07, 32.23, 27.96, 22.83, 22.31, 21.85, 20.50; FABMS (m/z) 582 (MH⁺).

The above compound, (14-A) (706mg, 1.21mmol), was dissolved in CH₂Cl₂ (5mL) and TFA (5mL) was added with stirring at RT. After 4 hours the solvent was evaporated and the residue chromatographed (SiO₂, gradient elution: 100% hexanes -> 100% EtOAc) to provide the mono methyl ester **Example 101** (623mg, 98%): ¹H NMR (300 MHz, Acetone-d₆), δ 9.79 (1H), 8.11 (1H), 7.7-7.9 (6H), 7.22 (2H), 4.81 (1H), 3.68 (3H), 3.15 (1H), 3.02 (1H), 2.86 (1H), 2.53 (1H), 2.0-2.2 (2H), 1.6-1.8 (1H), 1.43 (1H), 1.26 (3H), 1.20 (3H), 0.81 (3H); ¹³C NMR (75 MHz, Acetone-d₆), δ 177.64, 173.39, 172.92, 165.03, 147.96, 138.68, 134.68, 134.11, 133.81, 131.70, 130.52, 129.97, 125.18, 120.62, 120.54, 56.90, 54.55, 53.88, 52.31, 47.16, 37.56, 33.40, 23.48, 23.00, 22.30, 21.66; ESMS (m/z) 526 (MH⁺).

Example 101 (605 mg, 1.15 mmol) was dissolved in H₂O (5mL) containing LiOH (138 mg, 5.76 mmol). This was stirred for 4 hours. The solution thus obtained was acidified with 2 N HCl (10 mL) and the precipitate filtered. The filter cake was washed with cold H₂O (3 mL) and then dried under high vacuum to provide **Example 102** (539 mg, 92%) as a white amorphous powder: ¹H NMR (300 MHz, DMSO-d₆), δ 10.66 (1H), 8.14 (1H), 7.85 (2H), 7.76 (2H), 7.57 (2H), 7.22 (2H), 4.4-4.5

(1H), 3.02 (1H), 2.88 (1H), 2.70 (1H), 2.3-2.4 (1H),
 1.8-2.0 (1H), 1.5-1.6 (1H), 1.2-1.4 (1H), 1.17 (3H),
 1.12 (3H), 0.67 (3H); ^{13}C NMR (75 MHz, DMSO- d_6), δ
 177.00, 173.17, 172.03, 163.90, 146.50, 137.19,
 134.04, 133.35, 132.69, 130.92, 129.38, 129.28,
 124.23, 119.44, 55.50, 53.59, 51.90, 45.95, 36.10,
 32.23, 22.30, 22.23, 21.72, 21.00; ESMS (m/z) 512
 (MH^+).

Scheme 15

10

Preparation 10-A

Scheme 15, 10-A

Stereochemistry = (1R-cis)

(1R-cis)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid 3-methyl ester 10-A ($\text{C}_{11}\text{H}_{18}\text{O}_4$).

15 To methanol (0.5L), cooled in an ice-water bath under nitrogen, is added acetyl chloride (50mL, 0.703mol) over 30 minutes. After stirring for 30 minutes (1R, 3S)-camphoric acid 15-A (100g, 0.5mol) was added in one portion. The camphoric acid dissolves over ca. 10
 20 minutes and the solution was allowed to warm slowly to room temperature and stir for 72 hours. Concentration

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in vacuo afforded a clear, pale yellow oil which was dissolved in ethyl acetate (0.6L). The solution was extracted with 0.5N aq. NaOH (4X0.35L). The combined aqueous phases were washed with pentane (0.35L) and the pH of the aq. layer was adjusted to ca. 4 with 1N aq. HCl. The aqueous layer was extracted with ether (4X0.35L) and the combined organic phases were concentrated in vacuo to give a colorless oil which slowly solidified to afford 96g (90%) of 10-A as a white crystalline solid. An analytical sample can be obtained by recrystallizing 10-A from ether-pentane (1:1) to provide 10-A as clear hexagonal plates.

MP: 76-77°C; ¹H-NMR (CDCl₃) δ 3.69(s, 3H), 2.79(m, 1H), 2.54(m, 1H), 2.20(m, 1H), 1.84(m, 1H), 1.54(m, 1H), 1.45(m, 1H), 1.27(s, 3H), 1.26(s, 3H), 0.86(s, 3H); IR(nujol): 3201, 2925, 1730, 1700, 1237, 1210, 1150, and 1110cm⁻¹; Anal: Calcd. for C₁₁H₁₈O₄: C, 61.66; H, 8.47; Found: C, 61.63; H, 8.75.

Preparation 15-C

Scheme 15, 15-C

Stereochemistry = (1R-cis)

(1R-cis)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid 1 (1,1-dimethylethyl)-3-methyl diester 15-C (C₁₅H₂₆O₄)

To 10-A (25g, 0.117mol) in a 500mL Parr bottle, cooled in a dry ice-iPrOH bath under nitrogen, was condensed isobutylene until the bottle was approximately 1/2 full. In a separate Erlenmeyer flask, ether (6mL) was cooled (dry ice-iPrOH bath) and conc. sulfuric acid (3mL) was added. The mixture was allowed to cool for ca. 5 minutes, then was slowly added via disposable pipet to the isobutylene-15-B mixture. The Parr bottle was transferred to the shaker apparatus and shaken for 12 hours (pressure ca. 35psi at the end of

101

12 hours). The bottle was surrounded by aluminum foil, dry ice was added to cool the bottle and contents, and the bottle was removed from the shaker when the pressure reading was ca. 0 psi. The isobutylene was condensed from the reaction vessel via a cold finger condenser over ca. 2 hours. The resulting thin oil was dissolved in pentane (0.5L), the organic phase was washed with water (2X0.25L), 0.5N aq. NaOH (2X50mL), and water (2X0.25L). The organic phase was concentrated in vacuo to provide 15-C as a clear colorless oil which slowly solidified at room temperature. Recrystallization from petroleum ether gave 15-C as a fine white crystalline solid (26.86g, 89%).

MP: 36-37.6°C; ¹H-NMR: (300MHz, CDCl₃): δ 3.68(s, 3H), 2.78(m, 1H), 2.52(m, 1H), 2.16(m, 1H), 1.78(m, 1H), 1.45(m, 1H), 1.45(s, 9H), 1.24(s, 3H), 1.17(s, 3H), 0.81(s, 3H).

Preparation 15-D

Scheme 15, 15-D

Stereochemistry = (1R-cis)

(1R-cis)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid 1-(1,1-dimethylethyl) ester 15-D (C₁₄H₂₄O₄)

To 15-C (10.25g, 0.38mol) in methanol (0.1L) was added in order water (0.1L, see considerable precipitation), LiOH di-hydrate (10g, 2.38mol), and 30% aq. hydrogen peroxide (0.1L). The mixture was warmed in a 90°C oil bath and allowed to stir for 20 hours. The mixture was cooled to room temperature and concentrated in vacuo to remove methanol and the residual white solid material was removed by filtration. The clear solution was washed with pentane (3X0.15L), the aqueous layer was cooled in an ice-water bath and carefully acidified to ca. pH 4 with 1N aq. HCl. The resulting

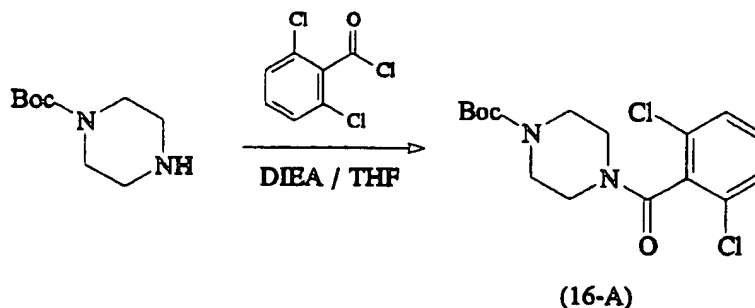
102

white precipitate was isolated by filtration, washed with water (3X0.1L) and air dried to afford 15-D (9.6g, 96%) as a fine white solid.

MP: 98-98.6°C; ¹H-NMR: (300MHz, CDCl₃): δ 2.82(1H), 2.50(1H), 2.13(1H), 1.79(1H), 1.46(9H) 1.45(1H), 1.28(3H), 1.18(3H), 0.89(3H); IR(nujol): 3075, 3025, 3006, 1719, 1689, 1270, 1249, 1164, and 851cm⁻¹; EI/MS : 200(3.8), 183(7.3), 164(7.1), 154(20.3), 136(14.6), 109(32.8), 57(base); Anal: Calcd. for C₁₄H₂₄O₄ · 0.18H₂O: C, 64.77; H, 9.46; Found: C, 64.79; H, 9.44; K.F. - Water: 0.86%.

Scheme 16

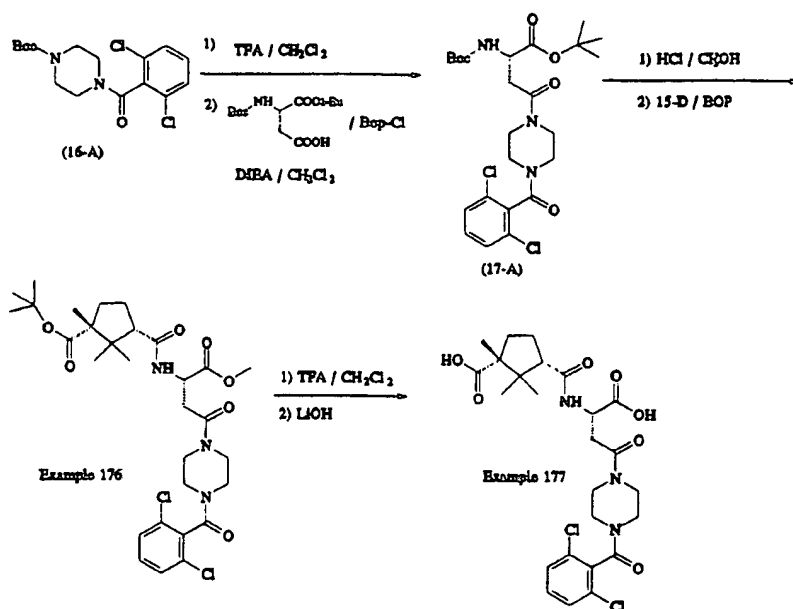
Synthesis of Intermediate 16-A



Boc-piperazine (1.9 gm, 10.4 mmol) was dissolved in THF (10 mL) and CH₂Cl₂ (1 mL) containing DIEA (5.6 mL, 32.2 mmol). To this solution 2,6-dichlorobenzoyl chloride (1.6 mL, 11.4 mmol) was added at 0°C. After stirring the reaction for 1 hour at 0°C, 1N HCl (30 mL) was added. The mixture was extracted with CH₂Cl₂ (2 x 20 mL) and the combined organics dried (Na₂SO₄), filtered and the solvent removed in vacuo. Chromatography of the residue (SiO₂, gradient elution, hexanes -> 30% EtOAc/hexanes) provided Intermediate (16-A) as an off white solid (3.6 gm, 98 %): mp = 157-159°C; ESMS (m/z) 359 (MH⁺).

Scheme 17

Examples 176 and 177



Intermediate 16-A (553 mg, 1.54 mmol) was dissolved in CH₂Cl₂ (5 mL) and treated with TFA (5 mL). After 2 hours the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (20 mL) containing DIEA (0.8 mL, 4.6 mmol). Boc-aspartic acid α t-butyl ester (534 mg, 1.85 mmol) was added with BOP-Cl (470 mg, 1.85 mmol). After stirring at RT for 24 hours the reaction was quenched with 1N HCl (25 mL). The mixture was extracted with CH₂Cl₂ (3 x 25 mL). The combined organics were dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by column chromatography (SiO₂, gradient elution, hexanes -> 50% EtOAc / hexanes) to provide the intermediate aspartate (17-A) (405 mg, 50%): ESMS (m/z) 530 (MH⁺).

To a methanolic solution of the above mentioned intermediate 17-A (0.2 g, 0.378 mmol), HCl gas was bubbled for 5 minutes and the reaction mixture was

left to stand overnight at room temperature. The methanol was evaporated and the residual gum was triturated with ether. The resultant solid was washed with ether and dried under high vacuum. The solid was

5 suspended in THF (5 mL), and 17-B (1R, 3S)-1-(tert-butoxycarbonyl)-1,2,2-trimethylcyclopentanecarboxylic acid (102 mg, 0.397 mmol), BOP (176 mg, 0.397 mmol) were added, followed by DIEA (0.207 mL, 1.19 mmol). The mixture was stirred overnight at room

10 temperature. The solvent was evaporated and the residue was partitioned between 1N HCl (5 mL) and EtOAc (15 mL). The organic layer was separated and washed successively with 1N HCl (5 mL), brine (5 mL), Sat. NaHCO₃ (2 x 5 mL), Sat. LiCl (2 x 5 mL), and dried

15 over MgSO₄. Evaporation of EtOAc produced a colorless solid, which was purified on silica (Chromatotron, hexane:EtOAc (1:1) as eluant) to provide **Example 176** (206 mg, 87%) as a colorless solid. ESMS: (m/z) 626 (MH⁺).

20 **Example 176** (0.18 g, 0.287 mmol) was dissolved in CH₂Cl₂ (1.0 mL) and TFA (1.0 mL). After stirring at room temperature for 1 hr the solvent was evaporated and the resultant gum triturated with ether. The solid was washed with ether and dried under vacuum to

25 provide [1S-[1 α (R^{*}),3 α]]- α -[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-4-(2,6-dichlorobenzoyl)- γ -oxo-1-piperazinebutanoic acid methyl ester as a colorless solid (0.14 g, 87%). ESMS (m/z) 570 (MH⁺).

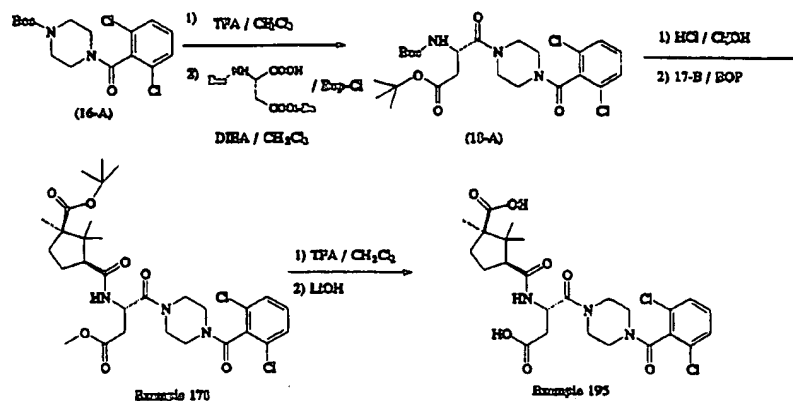
30 To a solution of the methyl ester obtained above (0.1 g, 0.18 mmol) in THF/CH₃OH (5 mL/1 mL) was added an aqueous (1 mL) solution of LiOH mono hydrate (19 mg, 0.378 mmol) and the mixture was stirred at room temperature for 2 h. The organics were evaporated and

35 the residue was taken up in 2 mL of water and acidified with citric acid. The solid was filtered,

washed with water and vacuum dried to provide **Example 177** (90 mg, 92%). ESMS (m/z) 556 (MH⁺).

Scheme 18

Examples 178 and 195



- 5 Intermediate 16-A (593 mg, 1.54 mmol) was dissolved in CH₂Cl₂ (6 mL) and treated with TFA (6 mL). After 2 hours the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (20 mL) containing DIEA (0.9 mL, 4.95 mmol). Boc-aspartic acid β t-butyl ester (573 mg, 1.98 mmol) was added with BOP-Cl (504 mg, 1.98 mmol). After stirring at RT for 24 hours the reaction was quenched with 1N HCl (15 mL). The mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were dried (Na₂SO₄),
- 10 filtered and the solvent removed in vacuo. The residue was purified by column chromatography (SiO₂, gradient elution, hexanes -> 50% EtOAc / hexanes) to provide the intermediate aspartate (18-A) (360 mg, 41 %): ESMS (m/z) 530 (MH⁺).
- 15
- 20 To a methanolic solution of the above mentioned intermediate (18-A) (0.25 g, 0.47 mmol), HCl gas was bubbled for 5 minutes and the reaction mixture was left to stand overnight at room temperature. The methanol was evaporated and the residual gum was

trituated with ether. The resultant solid was washed with ether and dried under high vacuum. The solid was suspended in THF (5 mL), and 15-D (1R, 3S)-1-(tert-butoxycarbonyl)-1,2,2-trimethylcyclopentanecarboxylic acid (127 mg, 0.495 mmol), BOP (219 mg, 0.495 mmol) were added, followed by DIEA (0.259 mL, 1.485 mmol). The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was partitioned between 1N HCl (5 ml) and EtOAc (15 ml). The organic layer was separated and washed successively with 1N HCl (5 ml), brine (5 ml), Sat. NaHCO₃ (2 x 5 ml), Sat. LiCl (2 x 5ml), and dried over MgSO₄. Evaporation of EtOAc produced a colorless solid, which was purified on silica (Chromatotron, hexane:EtOAc (1:1) as eluant) to provide **Example 178** (249 mg, 77%) as a colorless solid. ESMS: (m/z) 626 (MH⁺).

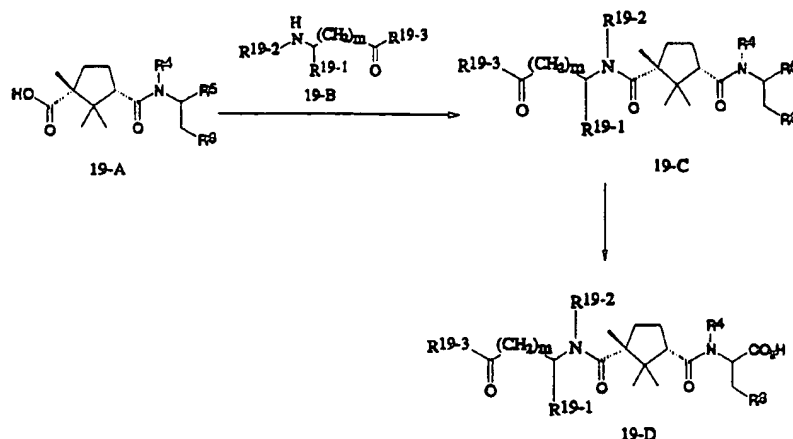
Example 178 (0.19 g, 0.303 mmol) was dissolved in CH₂Cl₂ (1.0 mL) and TFA (1.0 mL). After stirring at room temperature for 1 hr the solvent was evaporated and the resultant gum triturated with ether. The solid was washed with ether and dried under vacuum to provide [1S-[1 α (R^o),3 α]]- β -[[[3-Carboxy-2,2,3-trimethylcyclopentyl)carbonylamino]-4-[2,6-dichlorobenzoyl)- γ -oxo-1-piperazinebutanoic acid methyl ester as a colorless solid (98 mg, 58%). ESMS (m/z) 570 (MH⁺).

To a solution of the methyl ester obtained above (60 mg, 0.105 mmol) in THF/CH₃OH (5 mL/1 mL) was added an aqueous (1 mL) solution of LiOH mono hydrate (9.5 mg, 0.221 mmol) and the mixture was stirred at room temperature for 2 h. The organics were evaporated and the residue was taken up in 2 ml of water and acidified with citric acid. The solid was filtered, washed with water and vacuum dried to provide **Example 195** (48 mg, 83%). ESMS (m/z) 556 (MH⁺).

Scheme 19

Examples 211, 212, 213, 214 and 215

R^{19-1} is defined in the same manner as R^{7-1} to include amino acids included in R^2 definition; R^{19-2} is proton or together with R^{19-1} cyclic amino acid; R^{19-3} is C_{1-6} alkyl -NH-, NH_2 or C_{1-6} alkyl-O- or OH.

**Preparation 19-C-1**Scheme 19, 19-C: wherein $R^4 = H$, $R^5 = CO_2CH_3$ $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$, $R^{19-2} = H$, $R^{19-1} = CH_3$, $R^{19-3} = OC(CH_3)_3$, $m = 0$ Stereochemistry = [1S-[1 α ,3 α (S*)]]

[1S-[1 α ,3 α (S*)]] N-3-[[[1-(1,1-dimethylethoxy)-
carbonylethyl)amino]carbonyl]-2,2,3-
trimethylcyclopentyl)carbonyl]-4-[(2,6-
dichlorobenzoyl)amino]-L-phenylalanine methyl ester
(19-C-1) ($C_{34}H_{43}Cl_2N_3O_7$)

A solution of (1S-cis)-N-[(3-Carboxy-2,2,3-
trimethylcyclopentyl)carbonyl]-4-[(2,6-
dichlorobenzoyl)amino]-L-phenylalanine methyl ester
19-A-1 (19-A: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-
Dichlorobenzoyl)amino]phenyl$) (0.468g, 0.85 mmol),
HATU (0.36g, 0.95 mmol), and diisopropylethyl amine (dry,
2 mL, 11.5 mmol) are stirred together with DMF

(dry, 5 mL) in a dry round bottom flask under a nitrogen atmosphere. After 30 minutes, D-alanine tbutyl ester hydrochloride (19-B, ($R^{19-1} = CH_3$, $R^{19-2} = H$, $R^{19-3} = t-BuO$, Stereochemistry D) (0.34g, 1.87 mmol) is added. After three days, the mixture is evaporated to dryness in vacuo to give a yellow oil which is mixed with methylene chloride (100 mL) and shaken with water (5 X 50 mL). The organic layer is then evaporated to dryness, giving an off-white solid.

Recrystallization from ethyl acetate / diethyl ether gives 19-C-1, as a white solid (0.428g, 74% yield). 1H NMR(300MHz, DMSO- d_6) δ 10.70(1H), 7.90(1H), 7.60-7.18 (8H), 4.48(1H), 4.15(1H), 3.57(3H), 2.95 (2H), 2.75(1H), 2.37(1H), 1.87(1H), 1.55(1H), 1.36(9H), 1.30(1H), 1.22(3H), 1.18 (3H), 1.09 (3H), 0.57(3H).

Preparation 19-C-2

Scheme 19, 19-C: wherein $R^4 = H$, $R^5 = CO_2CH_3$

$R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$

$R^{19-2} = H$, $R^{19-1} = CH_3$, $R^{19-3} = OH$, $m = 0$

Stereochemistry = [1S-[1 α ,3 α (S*)]]

[1S-[1 α ,3 α (S*)]]-N-[[3-[[1-Carboxyethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester (19-C-2) ($C_{30}H_{35}Cl_2N_3O_7$)

Di-ester 19-C-1 is stirred overnight with trifluoroacetic acid (5 mL) and then the mixture is diluted with toluene (100mL) followed by evaporation to dryness in vacuo, giving acid 19-C-2 as a pale brown oil (0.34g, 90% yield).

1H NMR(300MHz, DMSO- d_6) δ 10.70(1H), 7.96 (1H), 7.57-7.10(8H), 4.47 (1H), 4.22 (1H), 3.57(3H), 2.95 (2H), 2.65(1H), 2.37(1H), 1.89(1H), 1.55 (1H), 1.30 (1H), 1.25(3H), 1.18(3H), 1.09 (3H), 0.57(3H); MS(ES+) m/z 619.8.

Preparation of Example 211

Scheme 19, 19-D: wherein $R^4 = H$, $R^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]\text{phenyl}$ $R^{19,2} = H$, $R^{19,1} = CH_3$, $R^{19,3} = OH$, $m = 0$ 5 Stereochemistry = [1S-[1 α ,3 α (S*)]]

[1S-[1 α ,3 α (S*)]]-N-[[3-[[[1-Carboxyethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine **Example 211**

10 ($C_{29}H_{33}Cl_2N_3O_7$)

A solution of LiOH \cdot H₂O (0.15g, 3.57mm) in H₂O (5mL) is added to a solution of 19-C-2 in methanol (5mL).

After overnight stirring, the solution is brought to pH7 with 1.2N aq. HCl (2 mL), evaporated in vacuo

15 until the methanol is gone, and shaken with diethyl ether (3X30mL). The aqueous layer is filtered, cooled in an ice bath and brought to pH2 using 1.2N aq. HCl. The resultant white precipitate is filtered, washed with water (100mL) and air dried to give **Example 211**

20 as a white solid (0.277g, 78% yield).

¹H NMR(DMSO-d₆) δ 10.67(1H), 7.76(1H), 7.57-7.44(5H), 7.31(1H), 7.20(2H), 4.42(1H), 4.22(1H), 3.03-2.82(2H), 2.64(1H), 2.36(1H), 1.89(1H), 1.54(1H) 1.32-1.26(4H), 1.19(3H), 1.09(3H), 0.58(3H); IR (nujol) 3293, 3261, 3078, 1740, 1672, 1612, 1562, 1551, 1527, 1518, 1429, 1415, 1334, 1276, 1197cm⁻¹; MS (ES-) m/z 606.3, 604.3; KF Water 7.76%.

Preparation 19-C-3

Scheme 19, 19-C: wherein $R^4 = H$, $R^5 = CO_2CH_3$,

$R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$,

$R^{19,2} , R^{19,1} = (CH_2)_3$, $R^{19,3} = NH_2$, $m = 0$

5 Stereochemistry = [1S-[1 α ,3 α (S*)]]

[1S-[1 α ,3 α (S*)]]-N-[3-[[2-(Aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester
 10 (19-C-3) ($C_{37}H_{37}Cl_2N_4O_6$)

In a similar manner to that reported for the synthesis of 19-C-1, 19-A-1 (19-A: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$) (0.55g, 1.00 mmol) is coupled to D-prolineamide (0.3g, 2.63 mmol) using HATU (0.40 g, 1.05 mmol) and diisopropylethyl amine (3 mL, 17.2 mmol) in dry DMF. After overnight stirring, the reaction mixture is evaporated to dryness in vacuo, giving a pale yellow oil which is stirred with ethyl acetate (50 mL). A precipitate soon formed and it is isolated by suction filtration to give 19-C-3 as a white solid (0.632g, 90% yield).
 15 1H NMR(DMSO- d_6) δ 10.67(1H), 7.95(1H), 7.58-7.48(5H), 7.19(2H), 7.10(1H), 6.65(1H), 4.45(1H), 4.18(1H), 3.70-3.30(1H), 3.57(3H), 2.90(2H), 2.58(1H), 2.28-
 20 1.40(9H), 1.25(3H), 1.12(3H), 0.73(3H).

Preparation of Example 212

Scheme 19, 19-D: wherein $R^4 = H$, $R^5 = CO_2Li$

$R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$,

$R^{19,2} , R^{19,1} = (CH_2)_3$, $R^{19,3} = NH_2$, $m = 0$

30 Stereochemistry = [1S-[1 α ,3 α (S*)]]

[1S-[1 α ,3 α (S*)]]-N-[3-[[2-(Aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-

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phenylalanine monolithium salt Example 212

(C₃₁H₃₅Cl₂N₄O₆Li)

A solution of LiOH·H₂O (0.2g, 4.8mmol) in H₂O (4mL) is added to a stirred solution of the methyl ester 19-C-3 (0.58g, 0.89mmol) in methanol (10mL). After overnight stirring, the mixture is evaporated in vacuo until the methanol is gone. The reaction mixture is then brought to pH 7 with 1N aq. HCl, filtered and the filtrate transferred to a C-18 reversed phase HPLC column and eluted with a 0-10% acetonitrile/water gradient. Evaporation is accomplished in vacuo to give the target compound as a white solid (0.445g, 78%yield).

¹H NMR (300MHz, DMSO-d₆) δ 10.55 (1H), 7.56-7.43 (5H), 7.04 (3H), 6.79 (1H), 6.62 (1H), 4.18 (1H), 3.92 (1H), 3.62 (1H) 3.43 (1H), 2.96 (2H), 2.44 (1H), 2.25-1.5 (8H), 1.23 (3H), 1.1 (3H), 0.75 (3H); IR (nujol) 3392, 3288, 3194, 3124, 3068, 1660, 1604, 1562, 1539, 1515, 1431, 1403, 1325, 799, 686cm⁻¹; MS (FAB) m/z (rel. intensity) 631 (M+H, 1), 659 (29), 653 (24), 643 (26), 639 (34), 637 (50), 279 (33), 133 (26), 109 (61), 70 (35), 23 (99); HRMS (FAB) m/z calcd for C₃₁H₃₆Cl₂N₄O₆ +H⁺ 631.2090, found 631.2086; KF Water: 9.90%.

Preparation 19-C-4

Scheme 19, 19-C: wherein R⁴ = H, R⁵ = CO₂CH₃,
R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl,
R¹⁹⁻², R¹⁹⁻¹ = (CH₂)₃, R¹⁹⁻³ = NH₂, m = 0
Stereochemistry = [1S-[1α,3α(R*)]]

[1S-[1α,3α(R*)]]-N-[3-[[2-(Aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenyl alanine methyl ester (19-C-4) (C₃₂H₃₇Cl₂N₄O₆)

In a similar manner to that reported for the synthesis of 19-C-3, 19-A-1 (19-A: R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-

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[(2,6-Dichlorobenzoyl)amino]-phenyl) (0.50g, 0.91 mmol) is coupled to L-prolineamide (0.2g, 1.75 mmol) using HATU (0.41 g, 1.08 mmol) and diisopropylethyl amine (1 mL, 5.74 mmol) in dry DMF (5mL). After overnight stirring, the mixture is evaporated to dryness in vacuo to give a yellow oil which is shaken with methylene chloride (100 mL) and water (50 mL); this gives a white precipitate which is filtered and the isolated solid is washed with water (3X50mL). Recrystallization from ethyl acetate gives 19-C-4 as a white solid (0.31g, 53% yield).
¹H NMR(DMSO-d₆): δ 10.70(1H), 7.92(1H), 7.50(5H), 7.19(2H), 7.04(1H), 6.74(1H), 4.48(1H), 4.11(1H), 3.58(3H), 3.47(1H), 2.92(2H), 2.56(1H), 2.35(1H), 2.10-1.45(8H), 1.24(3H), 1.09(3H), 0.71(3H);
 MS(ES+, m/z) 644.9.

Preparation of Example 213

Scheme 19, 19-D: wherein R⁴ = H, R⁵ = CO₂Na
 R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl,
 R¹⁹⁻², R¹⁹⁻¹ = (CH₂)₃, R¹⁹⁻³ = NH₂, n = 0
 Stereochemistry = [1S-[1α(S*),3α(S*)]]

[1S-[1α,3α(R*)]]-N-[3-[[2-(Aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,2,3-trimethylcyclopentyl]-carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine monosodium salt ~~Example~~ 213
 (C₃₁H₃₅Cl₂N₄O₆Na)
 The ester 19-C-4 (0.258g., 0.4mmol) is hydrolyzed in a manner similar to that described above for Example 212. The reaction mixture is then brought to pH 7, filtered and the filtrate transferred to a C-18 reversed phase HPLC column and eluted with a 0-10% acetonitrile/0.01% aqueous Na₂CO₃ gradient. Evaporation is accomplished in vacuo to give the target compound as a white solid (0.2g, 76% yield).

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¹H NMR (300MHz, DMSO-d₆): δ 10.57(1H), 7.56-7.44(4H), 7.02(3H), 6.77(2H), 4.10(1H), 3.91(1H), 3.6(1H), 3.50(1H), 3.95(1H), 2.44(1H), 2.10-1.50(7H), 1.23(3H), 1.07(3H), 0.73(3H); IR (nujol) 3392, 3288, 3194, 3124, 3068, 1660, 1604, 1562, 1539, 1515, 1431, 1403, 1325, 799, 686cm⁻¹; MS (FAB) m/z (rel. intensity) 631 (M+H, 1), 659 (29), 653 (24), 643 (26), 639 (34), 637 (50), 279 (33), 133 (26), 109 (61), 70 (35), 23 (99); HRMS (FAB) calcd for C₃₁H₃₆Cl₂N₄O₆ +H⁺ 631.2090, found 631.2086; KF Water: 9.90%.

Preparation 19-C-5

Scheme 19, 19-C: wherein R⁴ = H, R⁵ = CO₂CH₃,
R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]phenyl,
R¹⁹⁻² = H, R¹⁹⁻¹ = H, R¹⁹⁻³ = OCH₃, m = 1

15 Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[2-(Methyloxycarbonyl)ethyl]amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester
20 (19-C-5) (C₃₁H₃₇Cl₂N₃O₇)
A solution of 19-A-1 (19-A: R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]phenyl) (0.6g, 1.09 mmol), HATU (0.5g, 1.32 mmol), and diisopropylethyl amine (dry, 2 mL, 11.5 mmol) are stirred together with DMF
25 (dry, 5 mL) in a dry round bottom flask under a nitrogen atmosphere. After 30 minutes, β-alanine methyl ester hydrochloride (19-B, R¹⁹⁻¹ = H, R¹⁹⁻² = H, R¹⁹⁻³ = CH₃O) (0.3g, 2.15 mmol) is added. After 18 hours, the mixture is evaporated to dryness in vacuo to
30 give a yellow oil which is mixed with ethyl acetate (150 mL) and shaken with water (50 mL). The organic layer is washed with water and brine (2X60mL, 5:1), satd. aq. NaHCO₃ (50mL), water and brine (60mL, 5:1), the organic layer is mixed with pentane (30mL) and is
35 cooled to -20°C (3 days). The resulting solid is

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isolated by filtration, washed with diethyl ether (2X50mL), and is air dried to give 19-C-5 as a white solid (0.63g, 91%).

¹H NMR(CDCl₃) δ 7.62(1H), 7.57(2H), 7.32(3H), 7.10
 5 (2H), 6.26 (1H), 5.81 (1H), 4.88 (1H), 3.75 (3H), 3.68 (3H), 3.48 (2H), 3.12 (2H), 2.51 (3H), 2.28 (2H), 1.80 (1H), 1.49 (1H), 1.26(3H), 1.15(3H), 0.74 (3H);
 MS(ES+) m/z 633.8.

Preparation of Example 214

10 Scheme 19, 19-D: wherein R⁴ = H,
 R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]phenyl,
 R¹⁹⁻² = H, R¹⁹⁻¹ = H, R¹⁹⁻³ = OH, m = 1
 Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[(2-Carboxyethyl)amino]carbonyl]-
 15 2,2,3-trimethylcyclopentyl]carbonyl]-4-[[[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (Example 214)
 (C₂₉H₃₃Cl₂N₃O₇)

To a solution of the dimethyl ester 19-C-5 (19-C: R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]-
 20 phenyl, R¹⁹⁻² = H, R¹⁹⁻¹ = H, R¹⁹⁻³ = OCH₃, n = 1, Stereochemistry = (1S-cis) - L) (0.52g, 0.82 mmol) in methanol (10mL) is added a solution of LiOH·H₂O (0.18g, 4.29 mmol) in water (4mL). After overnight stirring, the reaction mixture is brought to pH 8
 25 using 1N aq. HCl and then evaporated to dryness in vacuo. The mixture is chromatographed on a reversed phase (C-18) HPLC column using a gradient (0 to 10% acetonitrile/(3% methanol in H₂O)). The selected eluant is evaporated to dryness and dissolved in water
 30 (50mL), cooled in an ice water bath, and brought to pH3 using 1N aq. HCl. The resultant white precipitate is isolated by suction filtration to give Example 214 as a white solid (0.43g, 85% yield).

¹H NMR(DMSO-d₆) δ 10.6 (1H), 7.91(1H), 7.55-7.42(5H),
 35 7.08(2H), 6.78(1H), 4.02 (1H), 3.10 (2H), 2.90 (2H),

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2.48 (1H), 2.25 (1H), 1.93 (3H), 1.56 (1H), 1.24 (1H),
 0.99 (3H), 0.93 (3H), 0.46 (3H); IR (nujol) 3327, 3080,
 1726, 1672, 1622, 1614, 1595, 1558, 1515, 1429, 1338,
 1279, 1262, 1197, 783 cm⁻¹; MS (FAB) m/z (rel.
 5 intensity) 606 (M+H, 99), 609 (24), 608 (69), 607
 (42), 606 (99), 605 (15), 517 (16), 254 (69), 175
 (16), 173 (25), 109 (51); HRMS (FAB) m/z calcd for
 C₂₉H₃₃Cl₂N₃O₇ +H⁺ 606.1774, found 606.1758.

Preparation 19-C-6

10 Scheme 19, 19-C: wherein R⁴ = H, R⁵ = CO₂CH₃,
 R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]phenyl,
 R¹⁹⁻², R¹⁹⁻¹ = (CH₂)₃, R¹⁹⁻³ = NHCH₃, m = 0
 Stereochemistry = [1S-[1α,3α(R⁶)]]

[1S-[1α,3α(R⁶)]]-4-[(2,6-Dichlorobenzoyl)amino]-N-[3-
 15 [[2-[(methylamino)carbonyl]-1-pyrrolidinyl]carbonyl]-
 2,2,3-trimethylcyclopentyl]carbonyl]-L-phenylalanine
 methyl ester (19-C-6) (C₃₃H₄₀Cl₂N₄O₆)

In a similar manner to that reported for the synthesis
 of 19-C-1, 19-A-1 (19-A: R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-
 20 [(2,6-Dichlorobenzoyl)amino]-phenyl) (0.53g, 0.96
 mmol), HATU (0.4g, 1.05 mmol), and diisopropylethyl
 amine (dry, 1.5 mL, 8.6 mmol) are stirred together
 with DMF (dry, 5 mL) in a dry round bottom flask under
 a nitrogen atmosphere. After 30 minutes, N-
 25 methylprolineamide hydrochloride (19-B: R¹⁹⁻¹, R¹⁹⁻² = CH₂,
 CH₂CH₂, R¹⁹⁻³ = NHCH₃, n=0, stereochemistry L) (0.5g, 3.04
 mmol) is added. After two days, the mixture is
 evaporated to dryness in vacuo to give a pale brown
 oil which is transferred to a silica gel column (20g)
 30 and eluted with a gradient from 0% to 10%
 methanol/chloroform to give, after solvent
 evaporation, 19-C-6 as a pale oil (0.55g, 86%)
¹H NMR (300MHz, DMSO-d₆) δ 10.68 (1H), 7.95 (1H), 7.58-
 7.44 (7H), 7.19 (2H), 4.48 (1H), 4.11 (2H), 3.57 (3H),

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3.06 (4H), 2.63 (3H), 2.46-1.69 (11H), 1.31 (3H),
1.12 (3H), 0.79 (3H).

Preparation of Example 215

Scheme 19, 19-D: wherein $R^4 = H$, $R^5 = CO_2Na$

5 $R^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]phenyl$,
 R^{19-1} , $R^{19-2} = CH_2CH_2CH_2$, $R^{19-3} = NHCH_3$, $m=0$
Stereochemistry = [1S-[1 α ,3 α (R*)]]

[1S-[1 α ,3 α (R*)]]-N-[3-[[2-[(Methylamino)carbonyl]-
1-pyrrolidinyl]carbonyl]-2,2,3-trimethyl-
10 cyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-
L-phenylalanine monosodium salt **Example 215**
($C_{32}H_{37}Cl_2NaN_4O_6$)

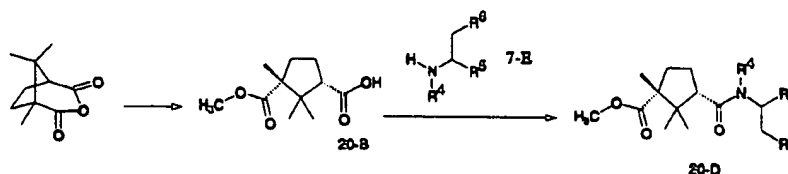
A solution of $LiOH \cdot H_2O$ (0.2g, 4.8mmol) in H_2O (6mL) is
added to a stirred solution of the methyl ester
15 19-C-6 (19-C: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]phenyl$) (0.53g, 0.8mmol) in
methanol (10mL). After overnight stirring, the
mixture is diluted with H_2O (50mL), evaporated in vacuo
until the methanol is gone. The reaction mixture is
20 then brought to pH 8 using 1N aq. HCl, filtered, and
the filtrate transferred to a C-18 reversed phase HPLC
column and eluted with a 10%-18% acetonitrile/0.02% aq
sodium bicarbonate gradient. The eluant is evaporated
to dryness, stirred with isopropanol (3X10mL) and
25 filtered through a sintered glass funnel. The
combined isopropanol filtrates are evaporated to
dryness, mixed with water and evaporated to dryness
again (2X10mL H_2O) to give **Example 215** as a white solid
(0.4g, 74% yield)

30 1H NMR (300MHz, $DMSO-d_6$) δ 10.57 (1H), 7.51 (6H),
7.04 (2H), 6.80 (1H), 4.18 (1H), 3.90 (1H), 3.55 (2H),
3.00 (2H), 2.53 (3H), 2.47 (1H), 2.12-1.50 (8H), 1.24 (3H),
1.09 (3H), 0.72 (3H).

HRMS (FAB) m/z calcd for $C_{32}H_{37}Cl_2N_4O_6Na_1 + H_1$ 667.2066;
35 found 667.2056.

Scheme 20

Example 205



Preparation 20-B

Scheme 20, 20-B

5 (1R-cis)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid 1-methyl ester (20-B)

A solution of (1R)-camphoric anhydride, prepared by the method of Bell, K.H. Aust. J. Chem. 1981, 34, 665-670, (5g, 27.44 mmol) in toluene (400 mL) in a round bottom flask is flushed with N₂ and then cooled in a dry ice/ ethanol bath. To this cooled solution is added (via dropwise addition) a one molar solution of potassium t-butoxide (30mL, 30 mmol) over a twenty minute period. After stirring overnight, the room temperature reaction mixture is again cooled on a dry ice/ ethanol bath. To the cooled solution is added methyl trifluoromethanesulfonate (3.5mL, 30.9 mmol). After an additional 12 hours of stirring, the reaction mixture is acidified with trifluoroacetic acid (50mL, 649 mmol), and is allowed to stir for another 16 hours. The mixture is then diluted with toluene (200mL), shaken with water (4 X 120 mL), and evaporated to dryness, giving 20-B as a pale brown solid (2.35g, 10.97 mmol, 40% yield).

25 ¹H NMR(300MHz, DMSO-d₆) δ 3.60 (s, 3H), 2.75 (m, 1H), 2.40 (m, 1H), 2.00 (m, 1H), 1.74 (m, 1H), 1.41 (m, 1H), 1.19(s, 3H), 1.15 (s, 3H), 0.70 (s, 3H).

Preparation 20-D

Scheme 20, 20-D: wherein $R^4 = H$, $R^5 = CO_2CH_3$

$R^6 = 4-[(2,6\text{-Dichlorophenyl)methoxy}]\text{-phenyl}$

Stereochemistry = [1*S*-cis]-L

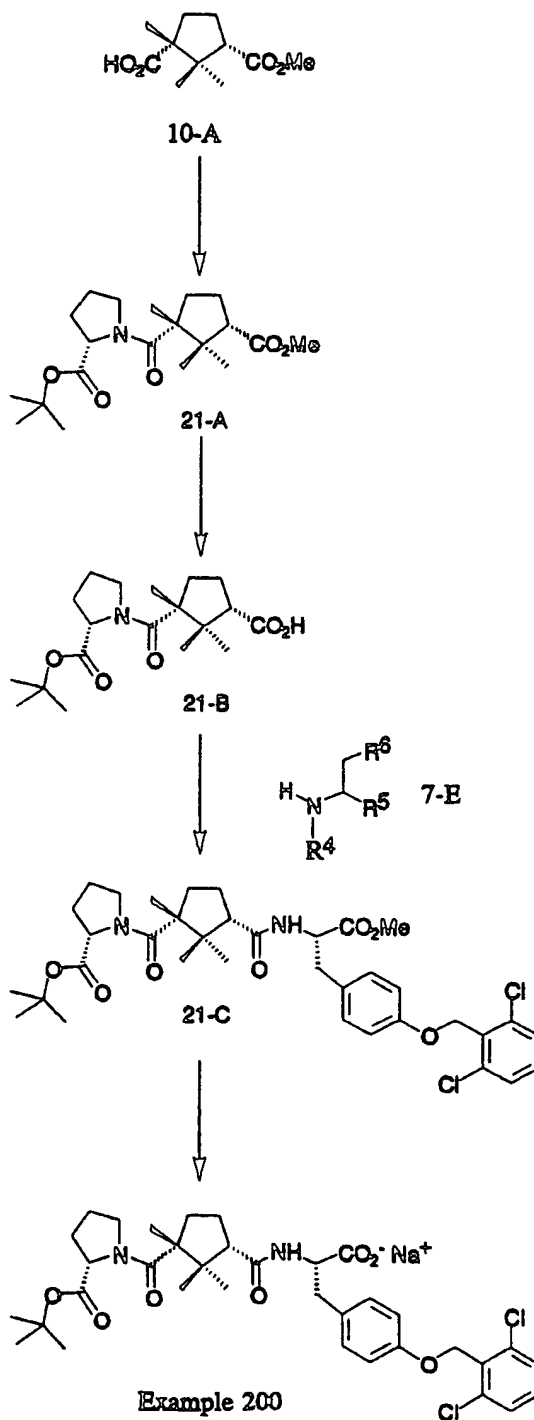
- 5 (1*S*-cis)-O-[(2,6-Dichlorophenyl)methyl]-N-[[3-(methoxycarbonyl)-2,2,3-trimethylcyclopentyl]-carbonyl]-L-tyrosine methyl ester (20-D)

A solution of camphoric acid methyl ester 20-B (0.35g, 1.63 mmol), EDC (0.35g, 1.83mmol), HOBT (0.25g, 1.85
10 mmol), 4-dimethylaminopyridine (0.05g, 0.41 mmol), in methylene chloride (10 mL) is stirred together in a 25 mL, 2-neck flask cooled in an ice water bath. To this mixture is added (2,6-dichlorophenyl)methyl)-L-tyrosine methyl ester hydrochloride (0.65g, 1.83
15 mmol), creating a thick, heterogeneous mixture which becomes homogeneous after addition of triethylamine (0.3mL, 2.15 mmol). After three days, the reaction mixture is diluted with methylene chloride (150mL) and shaken with water (2X 100 mL), aqueous HCl (0.5N,
20 2X100mL), water (3X100mL), aqueous NaHCO₃ (2X100mL), and water (1X100mL). The organic layer is then evaporated to dryness, giving 20-D as an off-white foam (0.7g, 78% yield).

¹H NMR(300MHz, CDCl₃) δ 7.38(m, 2H), 7.26(m, 1H),
25 7.05(m, 2H), 6.96(m, 2H), 5.76(m, 1H), 5.25(s, 2H), 4.88(m, 1H), 3.75(s, 3H), 3.67(s, 3H), 3.17-3.03(m, 2H), 2.61-2.50(m, 2H), 2.26-2.13(m, 1H), 1.84-1.70(m, 1H), 1.54-1.45(m, 1H), 1.22(s, 3H), 1.19(s, 3H), 0.76(s, 3H).MS(ES+) m/z 549.8

Scheme 21

Example 200



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(1R-cis)-N-[[3-Methoxycarbonyl-1,2,2-trimethylcyclopentyl]carbonyl-L-proline 1,1-dimethylethyl ester 21-A

The camphoric acid mono ester 10-A (1.41g, 6.58mmol)
5 in DMF(dry, 5 mL) in a dry flask under N₂ is cooled in
an ice water bath. Diisopropylethyl amine (4.6mL,
26.41mmol) is added followed by HATU (2.6g, 6.83mmol).
After thirty minutes, L-proline t-butyl ester (1.3mL,
7.44mmol) is added. After overnight stirring, the
10 mixture is evaporated to dryness, to give a pale
yellow oil. Recrystallization from CHCl₃ to give 21-A
as a white solid (1.6g, 66% yield). ¹H NMR(300MHz,
CDCl₃) δ 4.32(1H), 3.67(3H), 3.59(2H), 2.71(1H),
2.39(1H), 2.20(2H), 2.10-1.70(5H), 1.43(9H), 1.38(3H),
15 1.20(3H), 0.93(3H); IR (nujol) 1741, 1733, 1617,
1430, 1396, 1359, 1343, 1218, 1202, 1185, 1174, 1157,
1127, 1014, 771cm⁻¹; MS (FAB) m/z (rel. intensity)
368 (M+H, 99), 369 (22), 368 (99), 312 (15), 280 (12),
197 (72), 169 (23), 137 (29), 109 (38), 70 (11), 57
20 (14). Anal. Calcd for C₂₀H₃₃NO₅: C, 65.37; H, 9.05;
N, 3.81. Found: C, 65.53; H, 8.88; N, 3.83.

(1R-cis)-[3-Carboxy-1,2,2-trimethylcyclopentyl]carbonyl-L-proline 1,1-dimethylethyl ester 21-B

25 To a solution of the diester 21-A (0.74g, 2.01mmol) in
methanol (5 mL) is added a solution of LiOH·H₂O (0.15g,
3.62mmol) in aq H₂O₂ (30%, 2mL) and water (5mL). After
overnight stirring, the mixture is evaporated until
all of the methanol is gone, and then cooled in an ice
30 water bath and brought to pH5 using 1N aq. HCl. The
resultant white precipitate is isolated by suction
filtration (with water washes, 3X30mL) to give 21-B as
a white solid (0.45g, 63 % yield).

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¹H NMR(300MHz, CDCl₃) δ 4.34(1H), 3.60(2H), 2.75(1H), 2.41(1H), 2.18(1H), 2.00-1.70(5H), 1.44(9H), 1.43(3H), 1.22(3H), 1.02(3H).

[1R-[1α,3α(S*)]]-N-[[3-[[[1-Carbomethoxy-2-[4-[(2,6-dichlorophenyl)methoxy]phenyl]ethyl]amino]carbonyl]-1,2,2-trimethylcyclopentyl]carbonyl]-L-proline 1,1-dimethylethyl ester **21-C**

A solution of the acid **21-B** (0.41g, 1.16mmol) in methylene chloride(20mL) under N₂ is cooled in an ice water bath. To this is added diisopropylethyl amine (2mL), EDC (0.26g, 1.36mmol), HOBT (0.19g, 1.41mmol) and dimethylaminopyridine (0.02g, 0.16mmol). Forty minutes later, **7-E-2** (**7-E**: R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-[(2,6-Dichlorophenyl)methoxy]phenyl) (0.45g, 1.27mmol) is added in one portion. After three days, the mixture is evaporated to dryness, giving a colorless oil which is mixed with THF (100mL) and water (50mL) and then shaken sequentially with water (2X50mL), aq. HCl (0.5N, 4X30mL), satd. aq. NaHCO₃ (2X50mL), and water (2X50mL). The organic layer is then evaporated to dryness, giving a colorless oil (0.91g) which is chromatographed on silica gel with 10% methanol/chloroform to give **21-C** as a white, foamy solid (0.57g, 70% yield).

¹H NMR(300MHz, CDCl₃) δ 7.31-6.87(7H), 5.80(1H), 5.18(2H), 4.81(1H), 4.25(1H), 3.67(3H), 3.53(2H), 3.04(2H), 2.44-1.58(9H), 1.37(9H), 1.33(3H), 1.13(3H), 0.90(3H). IR (nujol) 1739, 1658, 1622, 1612, 1585, 1511, 1439, 1298, 1241, 1204, 1177, 1153, 1122, 1017, 768cm⁻¹; MS (FAB) m/z (rel. intensity) 689 (M+H, 24), 689 (24), 520 (69), 519 (32), 518 (99), 336 (44), 280 (21), 161 (24), 159 (40), 109 (75), 57 (22).

Preparation of Example 200

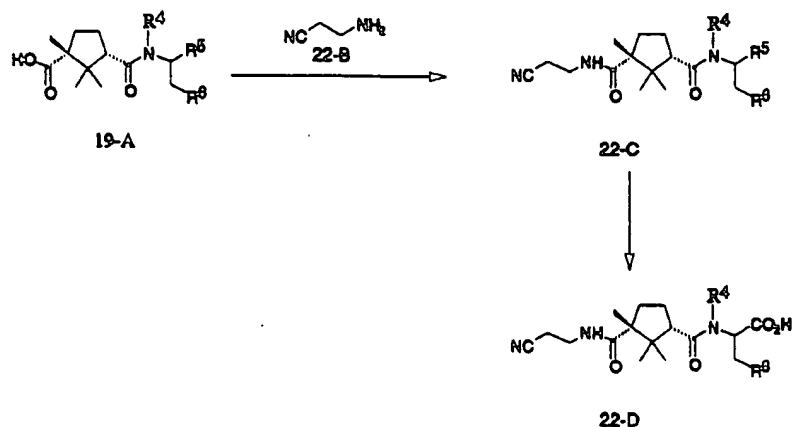
[1R-[1 α ,3 α (S*)]]-N-[[3-[[[1-Carboxy-2-[4-[(2,6-dichlorophenyl)methoxy]phenyl]ethyl]amino]carbonyl]-1,2,2-trimethylcyclopentyl]carbonyl]-L-proline 1,1-dimethylethylester, monosodium salt (Example 200)

To a solution of 21-C (0.43g, 0.62mmol) in methanol is added a solution of LiOH \cdot H₂O (0.083g, 1.98mmol) in aqueous H₂O₂ (30%, 3mL) plus H₂O (3 mL). After overnight stirring, the mixture is diluted with water (50mL) and evaporated in vacuo until the methanol is gone. The aqueous layer is then washed with diethyl ether (3X30mL) and brought to pH6 using 1 N aq. HCl. The resultant white precipitate is isolated by suction filtration to give a white solid (0.4g). This is stirred overnight with NaHCO₃ (0.1g, 1.2mmol) in H₂O (5mL). The aqueous solution is brought to pH7-8 using 1 N HCl and then transferred to a C-18.HPLC column and eluted with a gradient of 0-12% acetonitrile/aq. Na₂CO₃ (0.02%). Evaporation is accomplished in vacuo to give [1R-[1 α ,3 α (S*)]]-N-[[3-[[[1-Carboxy-2-[4-[(2,6-dichlorophenyl)methoxy]phenyl]ethyl]amino]carbonyl]-1,2,2-trimethylcyclopentyl]carbonyl]-L-proline 1,1-dimethylethylester, monosodium salt as a white solid (0.2g, 46%)

¹H NMR(DMSO-d₆) δ 7.55-7.41(3H), 7.01(2H), 6.82(2H), 6.80(1H), 5.13(2H), 4.08(1H), 3.90(1H), 3.65(1H), 3.40(1H), 3.31(3H), 2.95(2H), 2.44(1H), 2.25-1.5(8H), 1.34(9H), 1.23(3H), 1.08(3H), 0.76(3H). IR (nujol) 3405, 1735, 1610, 1565, 1511, 1439, 1299, 1240, 1195, 1175, 1153, 1093, 1018, 779, 769cm⁻¹; MS (FAB) m/z (rel. intensity) 675 (M+H, 0), 720 (27), 701 (25), 700 (67), 699 (39), 698 (99), 336 (32), 280 (23), 159 (20), 109 (53), 23 (28). HRMS (FAB) m/z calcd for C₃₅H₄₄Cl₂N₂O₇ +Na 697.2424, found 697.2418.

Scheme 22

Example 216



Preparation 22-C-1

Scheme 22, 22-C: wherein $R^4 = \text{H}$, $R^5 = \text{CO}_2\text{CH}_3$,

$R^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]\text{phenyl}$,

Stereochemistry = (1*S*-cis) - L

(1*S*-cis)-N-[[3-[[[(2-Cyanoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester
 10 (22-C-1) ($\text{C}_{30}\text{H}_{34}\text{Cl}_2\text{N}_4\text{O}_5$)
 A solution of 19-A-1 (19-A: $R^4 = \text{H}$, $R^5 = \text{CO}_2\text{CH}_3$, $R^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]\text{phenyl}$) (0.5g, 0.91 mmol), HOBT (0.12g, 0.91 mmol), and DCC (0.18g, 0.91mmol) are stirred together in CH_2Cl_2 (dry, 10 mL) in a dry round
 15 bottom flask under a nitrogen atmosphere. After 30 minutes, 2-cyanoethyl amine 22-B (0.064g, 0.91 mmol) is added. After 24 hours a precipitate is observed and methanol (5mL) is added to achieve a homogenous solution and an additional portion of 2-cyanoethyl
 20 amine 22-B (0.064g, 0.91 mmol) is added. After an additional 8 days of stirring the solvent is removed in vacuo and the residue is dissolved in THF and

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purified by chromatography on a column of silica gel to give 22-C-1 (0.42g, 78%) as a white solid.

¹H-NMR (300 MHz, MeOH-d₄): δ 7.58(2H), 7.43(3H),

7.22(2H), 5.48(1H), 4.72(1H), 3.69(3H), 3.58(2H),

5 3.29(1H), 3.02(1H), 2.65-2.77(3H), 2.40(1H), 2.04(1H),
1.76(1H), 1.47(1H), 1.27(3H), 1.20(3H), 0.74(3H);

Anal. Calcd for C₃₀H₃₄Cl₂N₄O₇·0.54H₂O : C, 58.95; H, 5.78;
N, 9.17; Found: C, 59.04; H, 5.75; N, 9.22; KF
Water 1.59%.

10

Preparation of Example 216

Scheme 22, 22-D: wherein R⁴ = H

R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]phenyl,

Stereochemistry = (1S-cis) - L

(1S-cis)-N-[[3-[[[(2-Cyanoethyl)amino]carbonyl]-

15 2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-
dichlorobenzoyl)amino]-L-phenylalanine (Example 216)
(C₂₉H₃₂Cl₂N₄O₅)

To the L-phenylalanine methyl ester 22-C-1 (22-C: R⁴ =
H, R⁵ = CO₂CH₃, R⁶ = 4-[(2,6-

20 Dichlorobenzoyl)amino]phenyl) (0.16g, 0.266mmol), in
methanol (10mL) is added a mixture of LiOH·H₂O
(0.056g, 1.33mmol), in H₂O (3mL). The mixture is
allowed to stir at room temperature for 2 hours, then
the solvent is removed in vacuo. The resulting solid
25 is dissolved in water (10mL) and the pH is adjusted to
ca. 2 with 1N aq. HCl to give a white precipitate.
the precipitate is isolated by filtration, washed with
water (10mL) and then dissolved in acetonitrile
(25mL). The organic phase is dried (Na₂SO₄) and the
30 solvent is removed in vacuo to give a sticky solid
which is dissolved in acetonitrile/water (25mL, 1:3)
and lyophilized to give 0.104g (67%) of the target
compound as a white solid.

¹H-NMR (300 MHz, MeOH-d₄): δ 7.82(1H), 7.57(2H),

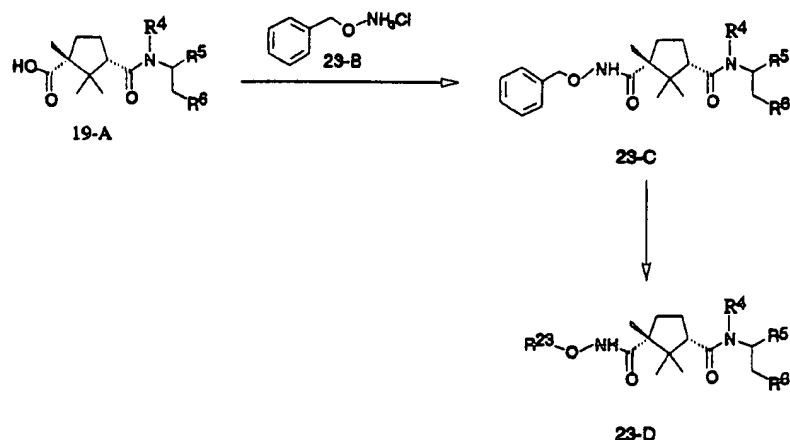
35 7.46(3H), 7.24(2H), 4.72(1H), 3.40(2H), 3.30(1H),

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2.99 (1H), 2.63-2.77 (3H), 2.40 (1H), 2.03 (1H), 1.74 (1H),
 1.48 (1H), 1.27 (3H), 1.20 (3H), 0.75 (3H); IR (nujol):
 3317, 3262, 1762, 1673, 1638, 1608, 1540, 1515, 1432,
 1325, 1203, 811, 801, 780 cm⁻¹; MS (FAB) m/z (rel.
 5 intensity) 587 (M⁺, base), 517 (12.4), 335 (9.8),
 252 (8.5), 235 (80); Anal. Calcd for C₂₉H₃₂Cl₂N₄O₇·2.14H₂O
 :C, 55.64; H, 5.84; N, 8.95; Found: C, 55.74; H,
 5.72; N, 8.99; KF Water 6.16%.

Scheme 23

10 Examples 217, 218 and 219

Preparation 23-C-1

Scheme 23, 23-C: wherein R⁴ = H, R⁵ = CO₂CH₃,
 R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]phenyl,
 Stereochemistry = (1S-cis) - L

15 (1S-cis)-4-[(2,6-Dichlorobenzoyl)amino]-N-
 [[2,2,3-trimethyl-3-
 [(phenylmethoxy)amino]carbonyl]cyclopentyl]carbonyl]-
 L-phenylalanine methyl ester (23-C-1) (C₃₄H₃₇Cl₂N₃O₆)
 A solution of 19-A-1 (19-A: R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-
 20 [(2,6-Dichlorobenzoyl)amino]phenyl) (0.5g, 0.91 mmol),
 HOBT (0.14g, 1.04 mmol), EDC (0.19g, 1.0 mmol),

triethylamine (0.46mL, 3.28mmol), and DMAP (0.012g, 0.1mmol) are stirred together in CH_2Cl_2 (dry, 15 mL) in a dry round bottom flask under a nitrogen atmosphere. Stir for 30 minutes at room temperature and

5 benzyloxyamine-HCl 23-B (0.26g, 1.64mmol) is added in one portion. The resulting mixture is allowed to stir for 72 hours at room temperature and the solvent is removed in vacuo. The residue is dissolved in CHCl_3 (50mL) and the solution is washed with 1N aq. HCl

10 (50mL), saturated aq. NaHCO_3 (50mL), and the organic layer is dried (MgSO_4). Concentration in vacuo gives the crude product as a sticky oil which is purified by flash chromatography on a column of silica gel (5% MeOH, 95% CH_2Cl_2) to give 0.27g (45%) of 23-C-1 (23-C: $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$, $\text{R}^6 = 4-[(2,6-$

15 Dichlorobenzoyl)amino]phenyl) as a white solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 8.13(1H), 7.57(2H), 7.49(1H), 7.35(6H), 7.10(2H), 5.78(1H), 4.89(2H), 3.76(3H), 3.14(2H), 2.47(1H), 2.18(2H), 1.30-1.90(4H),

20 1.27(3H), 1.15(3H), 0.80(3H); Anal. Calcd for $\text{C}_{34}\text{H}_{37}\text{Cl}_2\text{N}_3\text{O}_6 \cdot 0.24\text{H}_2\text{O}$: C, 61.97; H, 5.73; N, 6.38; Found: C, 62.02; H, 5.75; N, 6.39; KF Water 0.66%.

Preparation of Example 217

Scheme 23, 23-D: wherein $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{H}$

25 $\text{R}^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]$ phenyl, $\text{R}^{23} =$ Phenylmethyl

Stereochemistry = (1S-cis) - L

(1S-cis)-4-[(2,6-Dichlorobenzoyl)amino]-N-[[2,2,3-trimethyl-3-

30 [[(phenylmethoxy)amino]carbonyl]cyclopentyl]carbonyl-L-phenylalanine (Example 217) ($\text{C}_{33}\text{H}_{35}\text{Cl}_2\text{N}_3\text{O}_6$)

A solution of 23-C-1 (23-C: $\text{R}^4 = \text{H}$, $\text{R}^5 = \text{CO}_2\text{CH}_3$, $\text{R}^6 = 4-[(2,6\text{-Dichlorobenzoyl})\text{amino}]$ phenyl) (0.075g, 0.11 mmol) in methanol (10mL) is treated with a solution of

35 LiOH-H₂O (0.024g, 0.57mmol) in water (5mL) over 5

minutes. The mixture is allowed to stir for 4 hours at room temperature, then the solvent is removed in vacuo. The crude residue is dissolved in water (10mL), is filtered through a sintered glass funnel and then
 5 the solution is brought to ca. pH 4 by the addition of 1N aq. HCl. The resulting solid is isolated by suction filtration, washed with water (2X10mL), and is then dissolved in acetonitrile-water (25mL, 1:3). The solution is frozen and lyophilized to give **Example 217**
 10 (23-D: $R^4 = H$, $R^5 = CO_2H$, $R^6 = 4-[(2,6-$
 Dichlorobenzoyl)amino]phenyl, $R^{23} = \text{phenylmethyl}$) (0.048g, 68%) as a white solid.
 1H -NMR (300 MHz, MeOH- d_4): δ 7.85(1H), 7.57(2H), 7.32-
 7.49(8H), 7.24(2H), 4.81(2H), 4.70(1H), 3.21(1H),
 15 2.98(1H), 2.69(1H), 2.24(1H), 1.98(1H), 1.72(1H),
 1.40(1H), 1.25(3H), 1.15(3H), 0.71(3H); IR(nujol):
 3264, 3195, 3063, 3032, 1731, 1658, 1607, 1562, 1538,
 1516, 1432, 1326, 1195, 800 cm^{-1} ; MS (ES+) m/z
 640 ($M+H^+$); Anal. Calcd for $C_{33}H_{35}Cl_2N_3O_6 \cdot 1.19H_2O$: C,
 20 59.87; H, 5.69; N, 6.35; Found: C, 59.70; H, 5.78;
 N, 6.37; KF Water 3.24%.

Preparation of Example 218

Scheme 23, 23-D: wherein $R^4 = H$, $R^5 = CO_2CH_3$,
 $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$, $R^{23} = H$
 25 Stereochemistry = (1S-cis) - L

(1S-cis)-4-[(2,6-Dichlorobenzoyl)amino]-N-[[3-
 [(hydroxyamino)carbonyl]-2,2,3-trimethyl-
 cyclopentyl]carbonyl]-L-phenylalanine methyl ester
 (Example 218) ($C_{27}H_{31}Cl_2N_3O_6$)
 30 A solution of 23-C-1 (23-C: $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-$
 [(2,6-Dichlorobenzoyl)amino]phenyl) (0.7g, 1.07mmol)
 in THF (120mL) is hydrogenated over $Pd(OH)_2$ (0.42g)
 under 46psi of hydrogen for 2.75 hours. The catalyst
 is removed by filtration through a pad of Celite®, the
 35 filter cake is rinsed with THF (75mL) and the solvent

is removed in vacuo to afford the crude product as a sticky solid. The crude material is purified by flash chromatography on a column of silica gel (EtOAc/HOAc, 99.9:0.1) to give **Example 218** (23-D: $R^4 = H$, $R^5 =$
5 CO_2CH_3 , $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$, $R^{23} = H$) (0.34g, 56%) as a white solid.
 1H -NMR (300 MHz, MeOH- d_4): δ 7.58(2H), 7.31-7.49(3H), 7.22(2H), 4.72(1H), 3.69(3H), 3.18(1H), 2.99(1H), 2.73(1H), 2.29(1H), 2.02(1H), 1.75(1H), 1.42(1H),
10 1.27(3H), 1.18(3H), 0.75(3H); IR(nujol): 3313, 3292, 3245, 3194, 3129, 3073, 1749, 1668, 1653, 1606, 1547, 1517, 1459, 1434, 1336, 1211, 1021, 801, 779 cm^{-1} ; MS (FAB) m/z (rel. intensity): 564($M^+ + H$, 71), 548(3), 531(base), 109(95).

15

Preparation of Example 219Scheme 23, 23-D: wherein $R^4 = H$, $R^5 = CO_2H$ $R^6 = 4-[(2,6-Dichlorobenzoyl)amino]phenyl$, $R^{23} = H$

Stereochemistry = (1S-cis) - L

(1S-cis)-4-[(2,6-Dichlorobenzoyl)amino]-N-[[3-
20 [(hydroxyamino)carbonyl]-2,2,3-trimethyl-
cyclopentyl]carbonyl]-L-phenylalanine (**Example 219**)
($C_{26}H_{29}Cl_2N_3O_6$)

A solution of **Example 218** (0.14g, 0.25mmol) in methanol (8mL) is treated with a solution of LiOH-H₂O
25 (0.053g, 1.27mmol) in water (4mL) over 15 minutes. The mixture is allowed to stir for 1.5 hours at room temperature, then the solvent is removed in vacuo. The residue is dissolved in water (25mL), the pH is
adjusted to ca. 4 with 1N aq. HCl, and the mixture is
30 extracted with ethyl acetate (3X25mL). The combined organic extracts are dried (MgSO₄), and concentrated in vacuo to give the crude material as a sticky solid. The crude product is dissolved in acetonitrile/water (25mL, 1:3), and the solution is frozen and
35 lyophylized to provide **Example 219** (23-D: $R^4 = H$, $R^5 =$

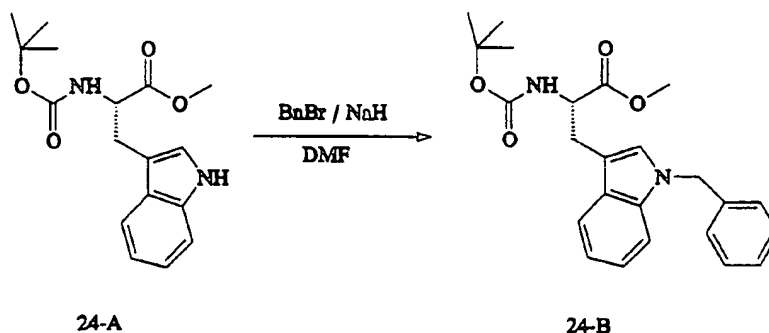
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CO₂H, R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl, R²³ = H) (0.098g, 71%) as a beige solid.

¹H-NMR (300 MHz, MeOH-d₄): δ 7.57(2H), 7.40-7.47(3H), 7.24(2H), 4.71(1H), 3.20(1H), 2.99(1H), 2.69(1H),
 5 2.29(1H), 2.03(1H), 1.75(1H), 1.43(1H), 1.28(3H), 1.18(3H), 0.76(3H); IR(nujol): 3262, 3197, 3127, 3070, 1725, 1657, 1607, 1584, 1562, 1535, 1516, 1432, 1326, 1234, 1194, 800, 781cm⁻¹; MS(FAB) m/z (rel. intensity): 550 (M⁺+H, 70), 517(75), 198(base); Anal. Calcd for
 10 C₂₆H₂₉Cl₂N₃O₆·0.95H₂O : C, 55.02; H, 5.49; N, 7.40; Found: C, 55.29; H, 5.93; N, 7.26; KF Water 3.02%.

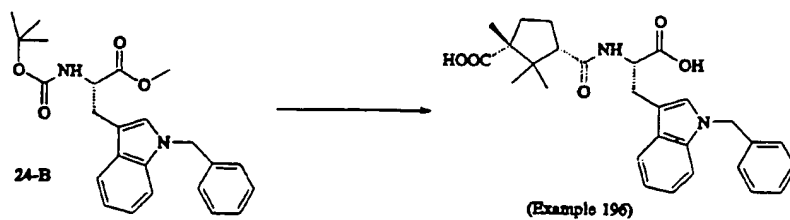
Scheme 24

Example 196



Boc-Tryptophan-O-methyl ester 24-A (636 mg, 2.00
 15 mmol, 1 eq) was dissolved in dry DMF. To this solution NaH (88 mg, 2.20 mmol, 1.1 eq) was added with evolution of H₂. To this mixture benzyl bromide (285 μL, 2.40 mmol, 1.2 eq) was added and the reaction stirred for 3 hours at room temperature. The reaction
 20 was quenched with brine (15 mL) and extracted with Et₂O (3 x 15 mL). The combined organics were dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by column chromatography (SiO₂, Hexanes to 30%EtOAc/Hexanes gradient elution) to
 25 provide 426 mg (52 %) of the benzyl indole 24-B.

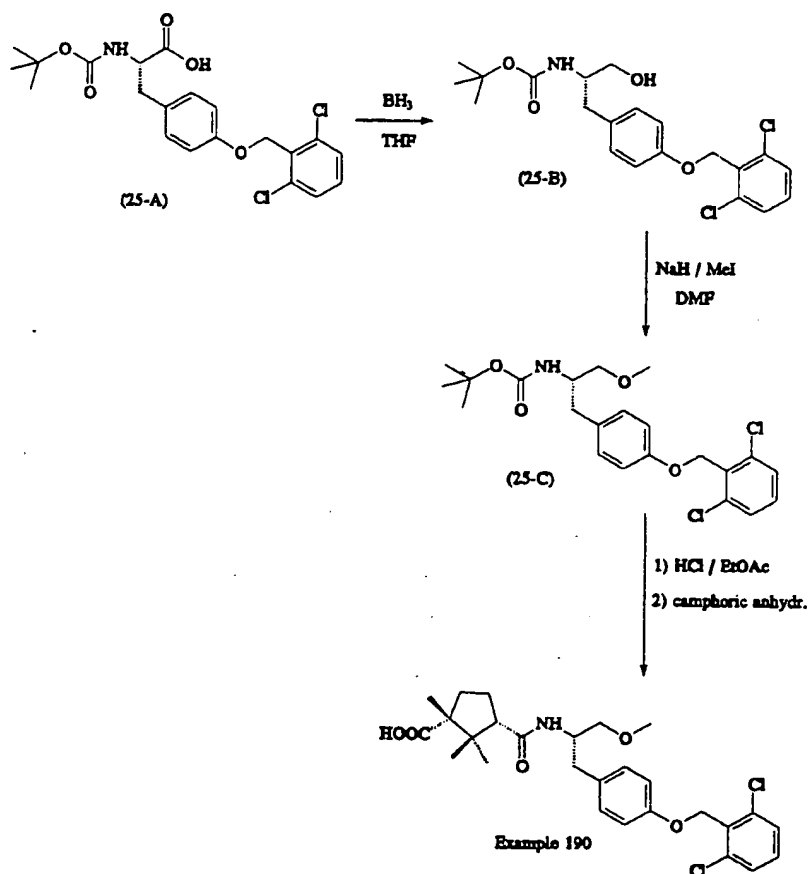
130



The final compound **Example 196** was produced as described in **Example 2**. ESMS (m/z): 475 ($M-H$)⁺.

Scheme 25

Example 190



The preparation of Example 190 is as follows.

Boc Tyr(2,6-dichlorobenzyl)-OH (25-A) (1.31 gm, 2.97 mmol) was dissolved in THF (5 mL) and cooled to -78°C under dry N₂. BH₃ THF (5.9 mL, 5.9 mmol, 1N) was added
5 and the reaction warmed slowly to room temperature with stirring for 3 hours. The reaction was cooled to 0°C and quenched with H₂O (1 mL) and warmed to room temperature. After the addition of 1 N HCl (25 mL), the mixture was extracted with EtOAc (3 x 25 ml) and
10 the combined organic phases were dried over Na₂SO₄. The solution was filtered, solvent evaporated and the residue chromatographed (SiO₂, gradient elution: 100% hexanes → 50% EtO Ac/hexanes) to provide the intermediate 25-B (665 mg, 53%): ESMS (m/z) 448
15 (M+Na)⁺.

The above compound, (25-B) (270 mg, 0.634 mmol), was dissolved dry DMF (5 mL) containing methyl iodide (51 µl, 0.824 mmol). To this solution was added NaH (28 mg, 0.697 mmol: in 60% oil) and the mixture was
20 stirred for 5 minutes. The reaction was quenched with the addition of H₂O (1 mL) followed by 1N HCl (10 ml). The mixture was extracted with EtOAc (3 x 15 mL) and the combined organics were dried over Na₂SO₄. The solution was filtered, solvent evaporated and the
25 residue chromatographed (SiO₂, gradient elution: 100% hexanes → 25% EtOAc/hexanes) to provide intermediate 25-C (130 mg, 47%): ESMS (m/z) 462 (M+Na)⁺.

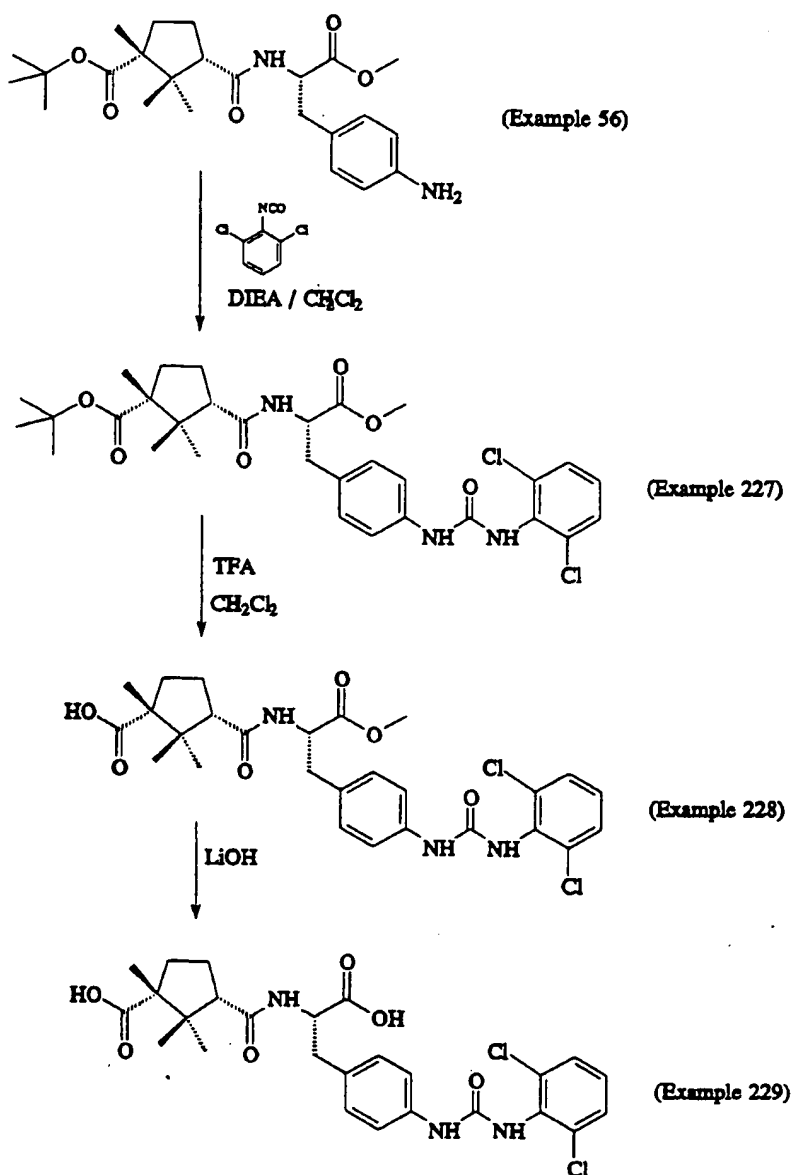
25-C (115 mg, 0.261 mmol) was dissolved in 3 N HCl/EtOAc (3 mL) and stirred for 1 h. The solvent was
30 removed under reduced pressure and dried thoroughly under high vacuum. The residue was dissolved in THF (5 mL) and DIEA (228 µL, 1.31 mmol) and (1R)-camphoric anhydride (57 mg, 0.314 mmol) was added. The reaction was warmed to 60°C with stirring for 48 h. After
35 cooling to room temperature, 1N HCl (15 mL) was added

and the mixture extracted with EtOAc (3 x 15 mL). The combined organics were dried over Na_2SO_4 , filtered and the solvent removed under reduced pressure. The residue was then chromatographed (SiO_2 , gradient elution: 100% hexanes \rightarrow 100% EtOAc) to provide

5 **Example 190** (113 mg, 83%): ESMS (m/z) 422 (MH^+).

Scheme 26

Examples 227-229



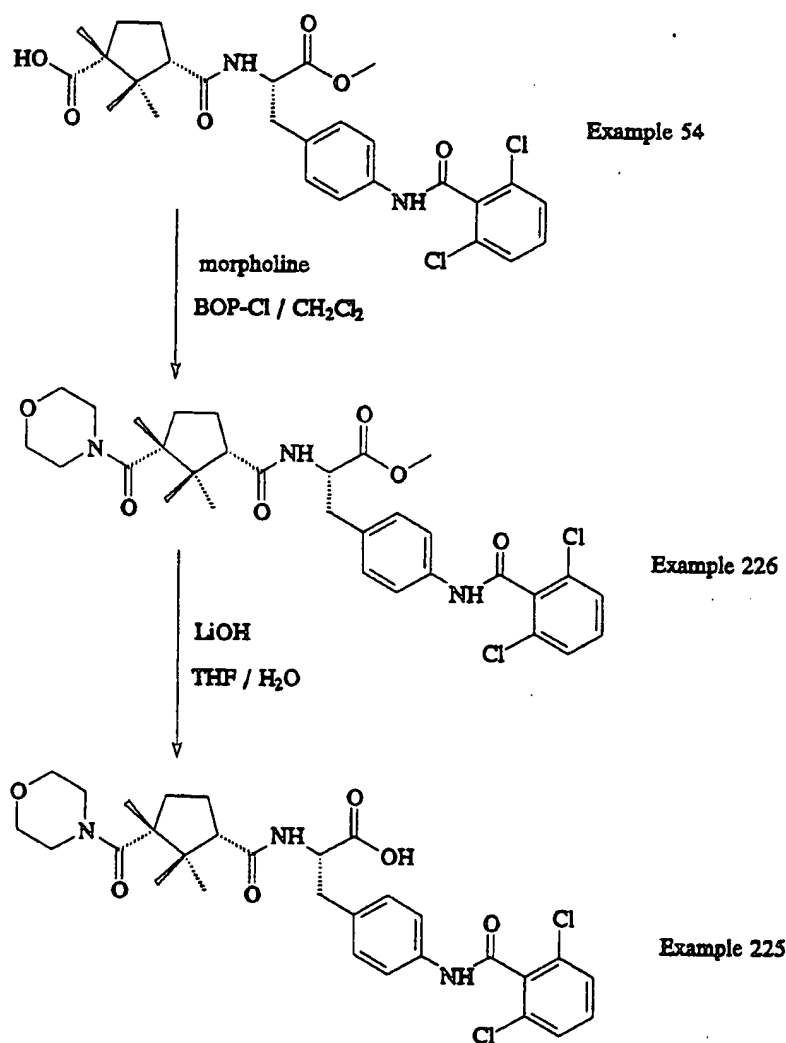
Example 56 (0.27 gm, 0.62 mmol) was dissolved in CH_2Cl_2 (10 mL) and 2,6-dichlorophenylisocyanate (0.18 gm, 0.94 mmol) and DIEA (327 μL , 1.86 mmol) was added and the reaction stirred overnight. After the addition of
5 1 N HCl (20 mL), the mixture was extracted with EtOAc (3 x 25 mL) and the combined organic phases were dried over Na_2SO_4 . The solution was filtered, solvent evaporated and the residue chromatographed (SiO_2 , gradient elution: 100% hexanes \rightarrow 33% EtOAc/hexanes)
10 to provide **Example 227** (310 mg, 82%): ESMS (m/z) 620 (MH^+).

Example 227 (250 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and TFA (1.5 mL). After 1 h, the solvent was removed and the residue triturated with Et_2O (3 x 5 mL)
15 to form a gum. The residue was purified by column chromatography (SiO_2 , gradient elution: 100% hexanes \rightarrow 25% acetone/hexanes) to provide **Example 228** (170 mg, 73%): ESMS (m/z) 564 (MH^+).

Example 228 (130 mg, 0.23 mmol) was dissolved in
20 THF/ CH_3OH (5 mL/1mL, respectively) and LiOH (22 mg, 0.53 mmol) was added in H_2O (1 mL). After 2 h the solvent was evaporated and the residue dissolved in H_2O (3 mL). The solution was precipitated with the addition of 1 N HCl (2 mL). The solvent was collected
25 by vacuum filtration and washed with cold H_2O (2x2 mL). The solid material was then thoroughly dried under high vacuum to afford **Example 229** (80 mg, 64%) as a white solid: ESMS (m/z) 550 (MH^+).

Scheme 27

Examples 225 and 226



Scheme 27 is as follows:

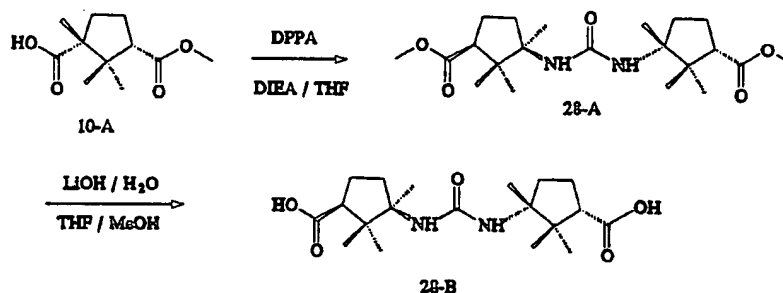
5 Example 54 (387 mg, 0.704 mmol) and morpholine (0.14 mL, 1.55 mmol) were dissolved in CH_2Cl_2 (15 mL). This solution was treated with BOP-Cl (215 mg, 0.845 mmol) and stirred under dry N_2 at room temperature. After 18 h the reaction was treated with 1 N HCl (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined

organics were dried over Na_2SO_4 , filtered and the solvent evaporated. The residue was then purified by column chromatography (SiO_2 , gradient elution: 100% hexanes \rightarrow 100% EtOAc) to provide Example 226 (160 mg, 37%) as a colorless oil: ESMS (m/z) 618 ($M+\text{Na}$)⁺.

The methyl ester (Example 226) (160 mg, 0.258 mmol), was dissolved in THF (5 mL) and LiOH (12 mg, 0.52 mmol) was added in H_2O (5 mL). After 4 h 1 N HCl (3 mL) was added and the precipitate collected by vacuum filtration washing with cooled H_2O (3 x 3 mL). The product was thoroughly dried under high vacuum to provide Example 225 (148 mg, 95%) as an amorphous powder: ESMS (m/z) 602 ($M-\text{H}$)⁻.

Scheme 28

Example 236



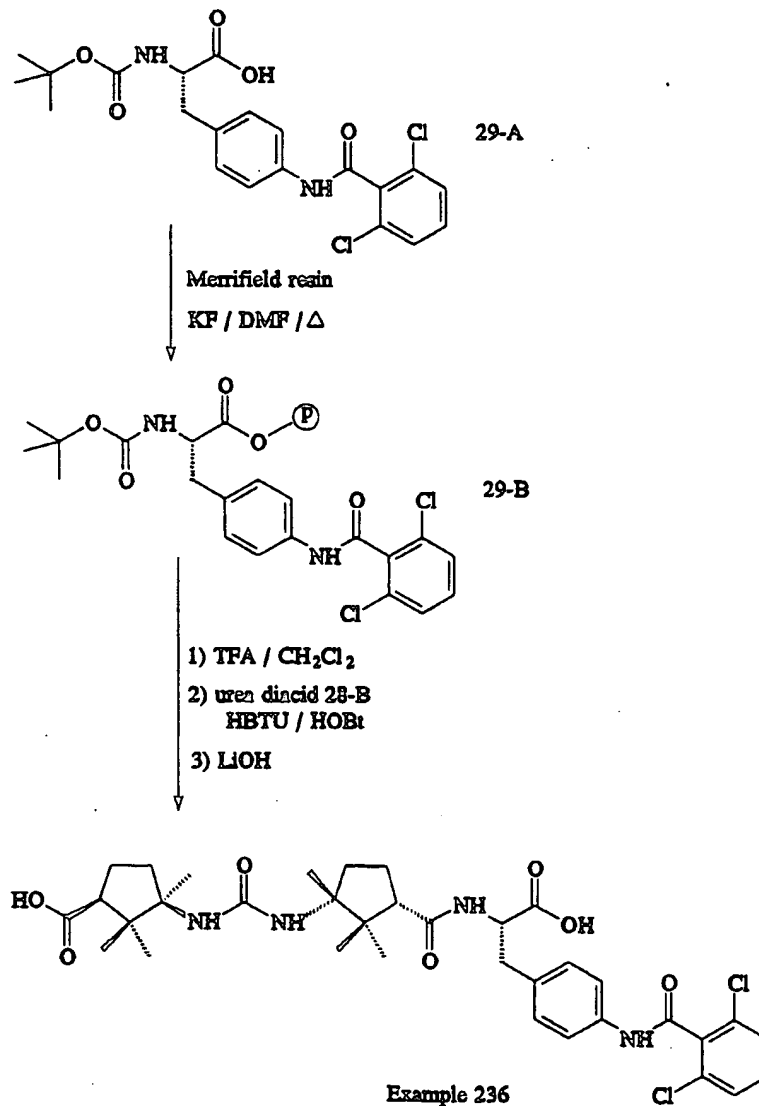
Intermediate used in solid phase synthesis

Intermediate Uron. Camphoric acid methyl ester (10-A) (2.15 g, 11.65 mmol) was dissolved in THF (25 mL). To this solution was added DPPA (diphenylphosphoryl azide) (3.33 g, 12.1 mmol) and DIEA (1.73 g, 13.4 mmol). The reaction was warmed at 45°C with stirring. After 2.5 h tert-butyl alcohol was added and heated at 85°C for an additional 2.5 h. The reaction was worked-up by removing the volatile components under reduced pressure. The residue was then purified by

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flash chromatography (SiO_2 , gradient elution: 2% EtOAc/hexanes \rightarrow 20% EtOAc/hexanes) to provide the symmetrical urea diester (28-A) (2.0 g, 43%): ESMS (m/z) 397 (MH^+).

- 5 The intermediate ester (28-A) (2 g, 5.0 mmol) was dissolved in THF/ CH_3OH (5 mL/2 mL, respectively) and LiOH (490 mg, 11.6 mmol) was added in H_2O (1 mL). After 2 h the solvent was evaporated, and the residue dissolved in H_2O (5 mL). The solution was precipitated
10 with the addition of 1 N HCl (15 mL). The solvent was collected by vacuum filtration and washed with cold H_2O (2 x 2 mL). The solid material was then thoroughly dried under high vacuum to afford the intermediate symmetrical urea diacid (28-B) (1.6 g, 89%) as a white
15 solid: ESMS (m/z) 369 (MH^+).

Scheme 29

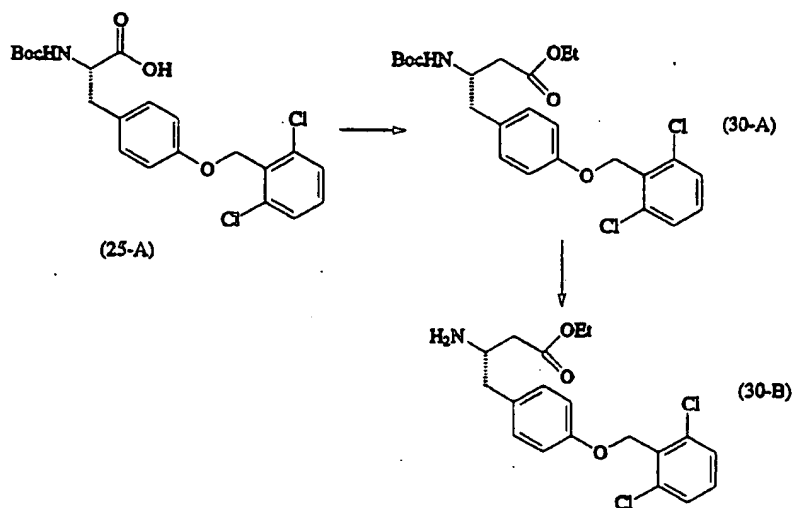
To a solution of N-(tert-butoxycarbonyl)-4-(2,6-dichlorobenzamido)-L-phenylalanine (29-A) (9.25g, 20.3 mmol) in DMF (100 mL) was added Merrifield resin

5 (10.0g, 10.0 meq/g) and anhydrous potassium fluoride (1.57g, 20.0 mmol). The reaction mixture was stirred for 1 day at 80°C and the resulting resin bound amino

acid was collected by filtration, washed sequentially with DMF (2 x 200 mL), 50% aqueous DMF (3 x 200 mL), CH₃OH (3 x 300 mL), CH₂Cl₂ (3 x 300 mL) and CH₃OH (3 x 100 mL) then dried in vacuo to provide the resin bound
5 N-(tert-butoxycarbonyl)-4-(2,6-dichlorobenzamido)-L-phenylalanine (29-B) (0.53 meq/g). Substitution of the Boc(L)Phe[4-(2,6-dichlorobenzamido)]-OH onto the resin was estimated using the picric acid method.

To the obtained resin (29-B) (150 mg, 0.107 mmol) was
10 added 50% TFA/CH₂Cl₂ (3 mL) and the mixture was shaken for 30 min. The resin was collected by filtration, washed sequentially with CH₂Cl₂ (2 x 10 mL), CH₃OH (2 x 10 mL), and CH₂Cl₂ (2 x 10 mL). To the washed resin was added the symmetrical urea diacid (28-B) (118 mg,
15 0.320 mmol), 0.5 M DMF solution of HBTU-HOBT (0.70 mL, 0.320 mmol), DIEA (0.139 mL, 0.799 mmol) and DMF (3.0 mL) and the mixture was vortexed for 2 hrs. at room temperature. The resin was collected by filtration, washed sequentially with DMF (2 x 10 mL), CH₂Cl₂ (2 10
20 mL), CH₃OH (2 x 10 mL), CH₂Cl₂ (2 x 10 mL). To the resin bound substrate was added THF (1.6 mL), CH₃OH (0.5 mL) and 2N LiOH (0.310 mL) and the mixture was shaken for 15 mins. The supernatant was collected by filtration and the resin washed with THF/5% CH₃OH (2 x
25 2 mL) and the combined filtrate was evaporated on a Pierce block evaporator. The concentrate was diluted with H₂O (1 mL) and the aqueous solution acidified with 1N HCl (1.5 mL). The precipitate was collected by centrifugation and the solid washed with H₂O (3 x 3
30 mL). The solid material was dried under high vacuum to furnish Example 236 (25 mg, 33%): ESMS (m/z) 701 (M-H)⁺.

Scheme 30



Scheme 2, III - a: wherein $R^4 = H$, $R^{5a} = -CH_2CO_2Et$,
 $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]-phenyl$ -
 Stereochemistry = (S)

5

(Intermediate for Examples 201 and 204)

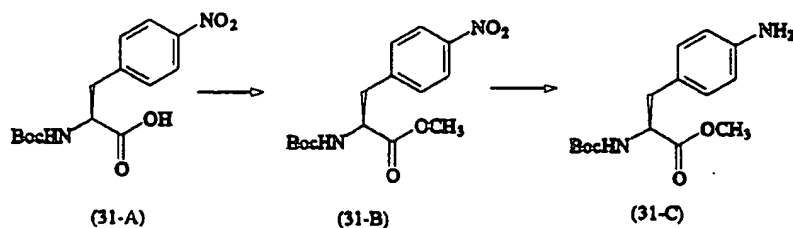
(S)-4-[(2,6-Dichlorophenyl)methoxy]- β -[[[(1,1-Dimethylethoxy)carbonyl]amino]benzenebutanoic acid ethyl ester (30-A) ($C_{24}H_{29}Cl_2NO_5$).

- 10 To a mixture of Boc-O-[(2,6-dichlorophenyl)-methyl]-L-tyrosine (25-A) (5.0 g, 11.36 mmol) and N-methylmorpholine in dry Et_2O at $-10^\circ C$ under Ar is added isobutyl chloroformate (1.49 mL, 11.36 mmol). The reaction is warmed to room temperature, stirred
- 15 for 1 h, and filtered. The filtrate is reacted at $0^\circ C$ with an excess of ethereal CH_2N_2 . The solution is stirred for 1 h at $0^\circ C$, and then is concentrated. The residue is dissolved in absolute EtOH, and a solution of $C_6H_5CO_2Ag$ (2.86 g, 12.38 mmol) in Et_3N (14 mL) is

added slowly. The resulting mixture is stirred for 1 h at room temperature under Ar and filtered. The filtrate is concentrated to a dark brown paste. The product is purified by silica flash chromatography (9:1 and 8:2 hexanes/EtOAc), from which is isolated 2.95 g (6.09 mmol, 54%) of 30-A: TLC R_f = 0.32 (7:3 hexanes/EtOAc); $[\alpha]_D$ (c = 0.9, CHCl_3) = -2° ; IR (mull) 3360, 2984, 2954, 2925, 2869, 2855, 1721, 1678, 1585, 1524, 1510, 1467, 1447, 1441, 1378, 1373, 1299, 1263, 1251, 1236, 1197, 1177, 1163, 1020, 1016, 783 cm^{-1} ; ^1H NMR δ 1.27 (3 H), 1.41 (9 H), 2.38-2.57 (2 H), 2.73-2.96 (2 H), 4.10-4.20 (3 H), 7.22-7.26 (1 H), 7.37 (2 H); MS (FAB) m/z 482, 426, 382, 364, 348, 338, 319, 294, 268, 216, 159, 133, 116, 107, 57; Anal. C 59.67, H 6.09, Cl 14.59, N 3.03 (calcd C 59.75, H 6.06, Cl 14.70, N 2.90).

(S)-4-[(2,6-Dichlorophenyl)methoxy]- β -aminobenzenebutanoic acid ethyl ester ($\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{NO}_3$). A solution of the Boc-aminoester (30-A) (0.74 g, 1.53 mmol) in 1:1 CH_2Cl_2 /TFA at 0°C under Ar is stirred for 30 min at 0°C and for 1.5 h at room temperature. It is concentrated, azeotroped thrice with toluene, and dried to give the aminoester (30-B) as a solid: TLC R_f = 0.15 (EtOAc); ^1H NMR (CHCl_3) δ 1.24 (3 H), 2.63-2.73 (2 H), 2.77-2.92 (1 H), 3.07-3.23 (1 H), 3.64-3.82 (1 H), 4.15 (2 H), 5.23 (2 H), 6.97 (2 H), 7.13 (2 H), 7.16-7.25 (1 H), 7.36 (2 H), 8.16 (2 H); MS (FAB) m/z 382, 365, 348, 294, 268, 224, 159, 133, 116, 70.

Scheme 31

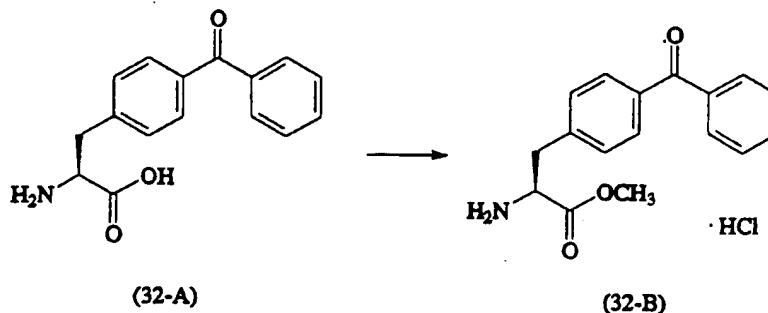


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Scheme 2, III - a: wherein $R^4 = [(\text{CH}_3)_3\text{CO}]C(O)-$,
 $R^{5a} = -\text{CO}_2\text{Me}$, $R^6 = 4\text{-aminophenyl-}$,
Stereochemistry = L

(Intermediate for Examples 208, 209, 210)

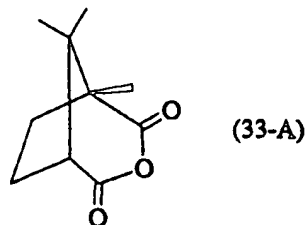
- 5 N-[(1,1-Dimethylethoxy)carbonyl]-4-nitro-L-phenylalanine methyl ester (31-B) ($\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_6$). A solution of N-Boc-4-nitrophenylalanine (31-A) (25.2 g, 81.28 mmol) and DMAP (0.82 g, 6.7 mmol) in dry DMF is cooled to 0 °C under Ar, and treated with MeOH (7.55
10 mL, 186 mmol) and DCC (18.975 g, 91.04 mmol). The reaction mixture is stirred overnight at room temperature and filtered. The filtrate is washed with satd NaHCO_3 and brine. The aqueous washes are back-extracted with CH_2Cl_2 . The organics are dried,
15 filtered and concentrated to a yellow solid. This product is purified by silica flash chromatography (3:1 hexanes/EtOAc) to give 24.6 g (75.85 mmol, 93%) of 31-B: TLC $R_f = 0.36$ (7:3 hexanes/EtOAc); ^1H NMR (CHCl_3) δ 1.41 (9 H), 3.12 (1 H), 3.28 (1 H), 3.73 (3
20 H), 4.63 (1 H), 5.05 (1 H), 7.31 (2 H), 8.16 (2 H); ^{13}C NMR δ 28.25, 38.38, 52.56, 54.08, 80.35, 123.67, 130.25, 144.03, 147.12, 154.90, 171.64.
4-Amino-N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine methyl ester (31-C) ($\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_4$). A solution of
25 the above product (2.87 g, 8.85 mmol) in MeOH is treated at room temperature under N_2 with 10% Pd/C (0.190 g), and hydrogenated at 40 psi for 3.5 h. The reaction mixture is filtered, and the filtrate is concentrated to give (31-C) as a dark foam: TLC $R_f =$
30 0.34 (1:1 EtOAc/hexane); ^1H NMR (CHCl_3) δ 1.42 (9 H), 2.97 (2 H), 3.48 (2 H), 3.70 (3 H), 4.51 (1 H), 4.93 (1 H), 5.05 (1 H), 6.61 (2 H), 6.90 (2 H); MS (EI) m/z 294, 238, 221, 207, 193, 177, 161, 135, 118, 106, 91, 77, 57.

Scheme 32

Scheme 2, III - a: wherein $R^4 = H \cdot HCl$, $R^{5a} = -CO_2CH_3$,
 $R^6 = 4\text{-benzoylphenyl-}$, Stereochemistry = L

(Intermediate to Examples 40, 191 and 197)

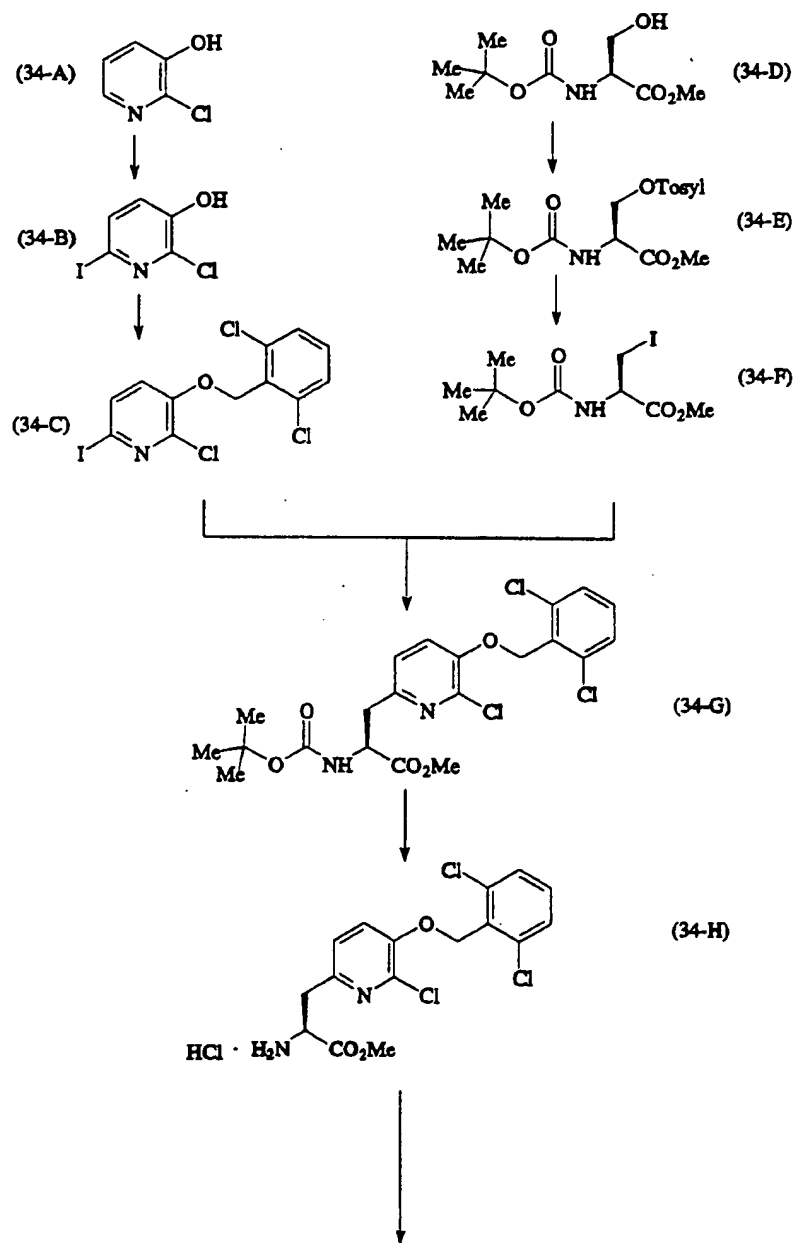
- 5 4-Benzoyl-L-phenylalanine methyl ester, HCl salt
 (32-B) ($C_{17}H_{17}NO_3 \cdot HCl$). To cold MeOH (100 mL) under N_2 is
 added AcCl (10 mL). The solution is stirred at room
 temperature for 30 min. 4-Benzoyl-L-phenylalanine
 (32-A) (0.99 g, 3.7 mmol) is treated with the
 10 methanolic HCl solution (60 mL) at room temperature
 for 26 h. The reaction mixture is concentrated to give
 1.05 g of the aminoester·HCl salt (32-B) as a solid:
 TLC (UV) $R_f = 0.40$ (95:5 $CHCl_3$ /MeOH); HPLC $t_R = 3.0$ min
 (isocratic 650:350:1 $CH_3CN/H_2O/TFA$); 1H NMR (CD_3OD) δ
 15 7.80-7.70 (4 H), 7.68-7.60 (1 H), 7.55-7.41 (4 H),
 4.84 (2 H), 4.44 (1 H), 3.82 (3 H), 3.44-3.27 (2 H);
 ^{13}C NMR (CD_3OD) δ 196.66, 168.86, 139.22, 137.29,
 136.91, 132.59, 130.34, 129.62, 129.35, 128.23, 53.56,
 52.39, 35.83.

Scheme 33

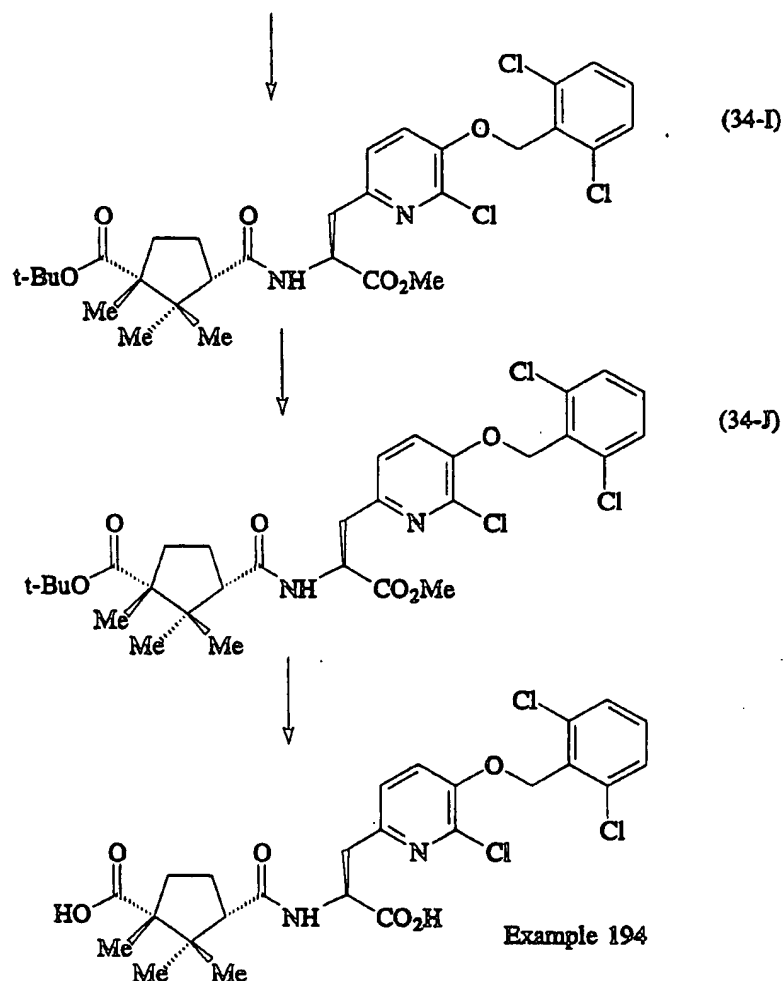
- (1S)-1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octane-2,4-dione [(1S)-camphoric anhydride] (33-A)
- 5 (1S-cis)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid) [(1S,3R)-camphoric acid] (1.0 g, 5 mmol) and acetic anhydride (10 mL) were heated at reflux for 3 h. The reaction was cooled and the solvent was removed on a rotovap (bath temp 60 °C). To the
- 10 remainder of the material, saturated NaHCO₃ (2 mL) was added. The aqueous portion was extracted with CH₂Cl₂ (3 x 5 mL), dried and concentrated in vacuo to 1.08 g. This was triturated with methyl-t-butyl ether to afford after filtering 0.94 g (103%) of (1S)-Camphoric anhydride (33-A): mp 222-223 °C; [α]_D +3.8° (c = 0.8, toluene); ¹H NMR (CDCl₃) δ 1.01, 1.10, 1.27, 1.89-2.35, 2.84; ¹³C NMR (CDCl₃) ppm 172.7, 170.0, 54.33, 53.8, 43.7, 33.5, 24.5, 20.8, 20.2, 14.1; IR (mineral oil mull) 2925, 1804, 1763, 1180, 1128, 1043, 983, 943
- 15 cm⁻¹; MS for C₁₀H₁₄O₃, m/z (relative intensity) 169 (1), 138 (37), 123 (17), 110 (16), 95 (100); . Anal. Calcd for C₁₀H₁₄O₃: C, 65.92; H, 7.75. Found: C, 65.86; H, 7.74.
- 20

Scheme 34

Example 194



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Preparation of Intermediate (34-B) (C_9H_7ClINO)

To a solution of 2-chloro-3-hydroxypyridine (34-A) (10.2 g, 78.7 mmol) and K_2CO_3 (38.87 g, 0.27 mol) in H_2O (120 mL) at rt is added I_2 (24.33 g, 95.8 mmol).
 5 The solution is stirred at rt for 4 h, and the reaction then is quenched with satd aqueous $Na_2S_2O_5 \cdot 5H_2O$. The pH of the reaction mixture is adjusted to pH 2 with 12 M aqueous HCl. The mixture is

extracted with EtOAc (3 x 100 mL), and the combined EtOAc portions dried (MgSO₄), filtered and concentrated to a yellow solid. Recrystallization of this solid from 120:25 heptane/EtOAc (145 mL) gives 11.2 g (43.8 mmol, 56%) of intermediate (34-B): IR 3113, 3068, 3056, 3021, 2991, 2955, 2925, 2871, 2855, 2832, 2808, 2749, 2668, 2601, 2530, 1554, 1457, 1398, 1304, 1289, 1226, 1086, 828, 711, 617 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.06 (1 H), 7.59 (1 H), 11.06 (1 H); ¹³C NMR (DMSO-d₆) δ 101.18, 127.02, 134.98, 138.07, 150.68; Anal. C 23.32, H 1.23, Cl 13.73, N 5.42 (calcd C 23.51, H 1.18, Cl 13.88, N 5.48).

Preparation of Intermediate 34-C (C₁₂H₇Cl₃INO).

To a mixture of (34-B) (5.11 g, 20.0 mmol), Ph₃P (5.30 g, 20.0 mmol) and 2,6-dichlorobenzyl alcohol (3.54 g, 20.0 mmol) in dry THF (100 mL) at 0 °C is added dropwise DEAD (3.15 mmol, 20.0 mmol). The reaction mixture is stirred an additional 1.5 h at 0 °C and 1.5 h at rt, and then is concentrated. The reaction product is purified by silica flash chromatography (85:15 hexanes/EtOAc) to give 7.61 g (18.36 mmol, 92%) of (34-C) as a white solid: TLC R_f = 0.57 (7:3 hexanes/EtOAc); ¹H NMR (DMSO-d₆) δ 5.34 (2 H), 7.48 (1 H), 7.55-7.63 (3 H), 7.85 (1 H); MS (ES) m/z 413.8, 327.9, 288.0, 255.9, 183.0, 150.9, 136.9.

Preparation of Intermediate (34-E) (C₁₆H₂₃NO₇S).

To a solution of *N*-Boc-L-serine methyl ester (34-D) (10.0 g, 45.6 mmol) in anhydrous pyridine (78 mL) at -10 °C under Ar is added TsCl (10.0 g, 52.4 mmol). The reaction mixture is stirred for 3 h at -10 °C, and then kept at -15 °C for 66 h. The reaction is quenched with ice, stirred for 2 h, and then extracted with EtOAc (4 x 300 mL). The combined EtOAc portions are washed with 0.2 M aqueous KHSO₄ (3 x 300 mL), H₂O (300 mL), satd aqueous NaHCO₃ (300 mL), and H₂O (300

mL); and then dried (Na_2SO_4), filtered and concentrated to a pale yellow-colored oil. The reaction product is purified by silica flash chromatography (3:1 hexanes/EtOAc) to give 13.0 g (34.8 mmol, 76%) of (34-E) as an off-white colored solid: TLC R_f = 0.25 (7:3 hexanes/EtOAc); IR 3400, 2407, 2313, 2291, 1928, 1741, 1708, 1513, 1350, 1245, 1174, 1159, 1060, 995, 941 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.41 (9 H), 2.44 (3 H), 3.69 (3 H), 4.28 (1 H), 4.39 (1 H), 4.49 (1 H), 5.29 (1 H), 7.34 (2 H), 7.75 (2 H); MS (FAB) m/z 747, 527, 374, 319, 318, 274, 146, 102, 57, 41, 29; Anal. C 51.41, H 6.32, N 3.87, S 8.27 (calcd C 51.46, H 6.21, N 3.75, S 8.59).

Preparation of Intermediate (34-F) ($\text{C}_9\text{H}_{16}\text{INO}_4$).

To a solution of (34-E) (12.82 g, 34.3 mmol) in dry acetone (40 mL), in an amber reaction flask at rt under Ar, is added dropwise a solution of NaI (7.73 g, 51.5 mmol) in dry acetone (40 mL). The reaction mixture is stirred at rt for 42 h, and then is concentrated. The residue is dissolved in CHCl_3 (300 mL). This CHCl_3 solution is extracted with H_2O (2 X 300 mL), aqueous 1 M $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (300 mL), and H_2O (3 X 300 mL); and then is dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. The product is purified by silica flash chromatography (4:1 hexanes/EtOAc) to give 9.49 g (28.8 mmol, 84%) of (34-F) as a white solid: TLC R_f = 0.52 (7:3 hexanes/EtOAc); ^1H NMR (CDCl_3) δ 1.45 (9 H), 3.56 (2 H), 3.79 (3 H), 4.51 (1 H); MS (FAB) m/z 330, 274, 230, 211, 170, 146, 102, 57, 41.

Preparation of Intermediate (34-G) ($\text{C}_{21}\text{H}_{23}\text{Cl}_3\text{N}_2\text{O}_5$).

To a dry amberized reaction flask under Ar, containing activated Zn dust (0.777 g, 11.89 mmol) and (34-F) (3.91 g, 11.9 mmol), is added dry THF (11.8 mL) and $\text{CH}_3\text{C}(\text{O})\text{N}(\text{Me})_2$ (11.8 mL). Residual O_2 is removed by

bubbling Ar through the suspension for 5 min. The reaction mixture is stirred at 65 ± 5 °C for 2 h, and then is cooled to 0 °C. The $\text{PdCl}_2[\text{P}(\text{Ph})_3]_2$ catalyst (0.41 g) is added, followed immediately by an O_2 -free solution of (34-C) (2.46 g, 5.94 mmol) in dry 1:1 THF/ $\text{CH}_3\text{C}(\text{O})\text{N}(\text{Me})_2$ (17.8 mL). The resulting reaction mixture is stirred at 65 ± 5 °C under Ar for 5 h. It is quenched with satd aqueous NH_4Cl (150 mL). The resulting mixture is extracted with EtOAc (3 x 300 mL). The combined EtOAc portions are washed with brine (300 mL), dried (Na_2SO_4), filtered and concentrated to a yellow-green colored oil. The product is purified by silica flash chromatography (3:1 hexanes/EtOAc) to give 1.90 g (3.88 mmol, 65%) of (34-G): TLC R_f = 0.32 (7:3 hexanes/EtOAc); IR 3391, 1734, 1702, 1567, 1561, 1508, 1439, 1287, 1256, 1225, 1214, 1198, 1179, 1167, 1152, 1099, 1087, 1070, 1022, 992, 989, 846, 784, 772, 718 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.31 (9 H), 2.94-3.03 (2 H), 3.60 (3 H), 4.32 (1 H), 5.30 (2 H), 7.28 (2 H); 7.45-7.58 (3 H), 7.76 (1 H); MS (ES) m/z 490.8, 434.8, 388.9.

Preparation of Intermediate (34-H) ($\text{C}_{16}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_3 \cdot \text{HCl}$).

A solution of (34-G) (1.90 g, 3.88 mmol) in 4 M HCl in 1,4-dioxane (35 mL) is stirred at rt under Ar for 20 h. The reaction mixture is concentrated, diluted with H_2O (40 mL), and extracted with Et_2O (3 x 40 mL). The Et_2O portions are discarded. The aqueous solution is lyophilized to give 1.39 g (3.26 mmol, 84%) of (34-H) as a beige-colored solid: ^1H NMR ($\text{DMSO}-d_6$) δ 3.27 (2 H), 3.72 (3 H), 4.37 (1 H), 5.32 (2 H), 7.37 (1 H), 7.48 (1 H), 7.58 (1 H), 7.81 (1 H), 8.62 (3 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 36.29, 51.98, 53.14, 66.74, 123.33, 125.04, 129.38, 131.21, 132.50, 136.63, 138.99, 147.02, 149.88, 169.75.

Preparation of Intermediate (34-I) ($C_{30}H_{37}Cl_3N_2O_6$).

To a reaction mixture containing acid (15-D) (0.513 g, 2.0 mmol), EDC (0.403 g, 2.06 mmol), HOBT (0.284 g, 2.10 mmol), DMAP (0.076 g, 0.62 mmol) and
5 (34-H) (0.878 g, 2.06 mmol) in CH_2Cl_2 (20.4 mL) at 0 °C is added Et_3N (1.02 mL, 7.24 mmol). The mixture is stirred for 2 h at 0 °C and 44 h at rt. It is diluted with CH_2Cl_2 (200 mL). The CH_2Cl_2 mixture is washed with H_2O (3 x 200 mL), 0.5 M aqueous HCl (2 x 200 mL), satd
10 aqueous $NaHCO_3$ (2 x 200 mL), and H_2O (2 x 200 mL). The combined aqueous washes are extracted with one portion of CH_2Cl_2 (200 mL). The combined CH_2Cl_2 portions are dried (Na_2SO_4), filtered, and concentrated to give a yellow-colored oil. The product is purified by silica
15 flash chromatography (3:2 hexanes/ $EtOAc$) to give 0.919 g (1.46 mmol, 73%) of (34-I): TLC R_f = 0.15 (7:3 hexanes/ $EtOAc$); 1H NMR ($CDCl_3$) δ 0.82 (3 H), 1.18 (3 H), 1.31 (3 H), 1.38-1.48 (1 H), 1.44 (9 H), 1.58-1.81 (1 H), 2.14-2.27 (1 H), 2.49-2.70 (2 H), 3.17 (1 H),
20 3.29 (1 H), 3.69 (3 H), 4.93 (1 H), 5.33 (2 H), 7.06 (2 H), 7.26-7.39 (4 H); ^{13}C NMR ($CDCl_3$) δ 14.19, 20.40, 21.93, 22.19, 22.91, 28.07, 32.36, 37.04, 46.41, 51.76, 52.28, 54.50, 56.78, 60.38, 61.17, 66.73, 80.07, 123.08, 123.23, 128.60, 130.92, 130.96, 137.08,
25 140.97, 149.43, 149.77, 171.71, 172.70, 175.11.

Preparation of Intermediate (34-J) ($C_{26}H_{29}Cl_3N_2O_6$).

To the solid (34-I) (0.910 g, 1.45 mmol) at 0 °C under Ar is added slowly TFA (9 mL). The resulting solution is stirred for 30 min at 0 °C and 2 h at rt.
30 The reaction mixture is concentrated *in vacuo*, thrice azeotroped with $PhCH_3$, and dried under vacuum to give (34-J) as an amber-colored foam: TLC R_f = 0.37 (750:250:5 hexanes/ $EtOAc/HCO_2H$); IR 3321, 3061, 1746, 1728, 1696, 1655, 1584, 1565, 1523, 1497, 1440, 1355,
35 1286, 1209, 1200, 1171, 1119, 1094, 1088, 995, 781, 769, 731, 717, 695 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.87 (3 H),

1.26 (3 H), 1.33 (3 H), 1.46-1.58 (1 H), 1.73-1.87 (1 H), 2.14-2.30 (1 H), 2.53-2.65 (2 H), 2.69 (1 H), 3.19 (1 H), 3.29 (1 H), 3.69 (3 H), 4.93 (1 H), 5.33 (2 H), 7.07 (1 H), 7.23-7.40 (4 H), 10.18 (1 H).

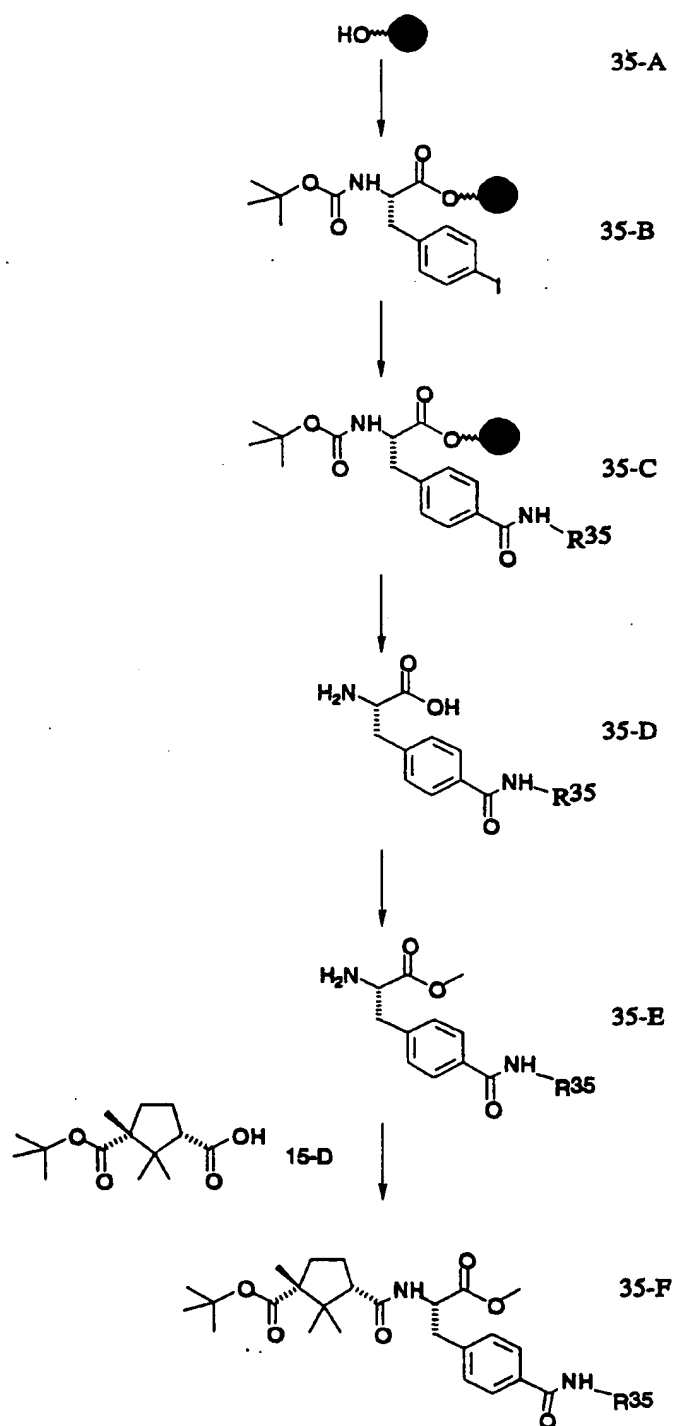
5 Preparation of Example 194 ($C_{26}H_{29}Cl_3N_2O_6$).

To a solution of (34-J) (0.908 g, 1.41 mmol) in THF (28.9 mL) is added a solution of LiOH·H₂O (0.291 g, 6.94 mmol) in H₂O (14.4 mL). The reaction mixture is stirred for 5 h, and then is diluted with H₂O (70 mL).
10 It is cooled to 0 °C, acidified with 1 M aqueous HCl, and extracted with EtOAc (3 x 200 mL). The combined EtOAc portions are washed with brine (200 mL), dried (Na₂SO₄), filtered and concentrated to a viscous
15 colorless oil. The product is purified by silica flash chromatography (200:50:1 hexanes/EtOAc/HCO₂H), azeotroped thrice from PhCH₃, dissolved in 1:1 CH₃CN/H₂O (40 mL), and lyophilized to give 0.752 g (1.35 mmol, 96%) of Example 194 as a white solid: mp 120-122 °C; TLC R_f = 0.28 (200:1 EtOAc/HCO₂H); IR 3323, 3064, 2730,
20 2668, 1714, 1700, 1648, 1584, 1564, 1522, 1440, 1354, 1284, 1235, 1198, 1162, 1118, 1096, 1089, 995, 862, 828, 780, 769, 716 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.63 (3 H), 1.09 (3 H), 1.12 (3 H), 1.24-1.37 (1 H), 1.46-1.58 (1 H), 1.78-1.94 (1 H), 2.27-2.43 (2 H), 2.62 (1 H),
25 2.96-3.14 (2 H), 3.31 (1 H), 4.57 (1 H), 5.30 (2 H), 7.29 (1 H), 7.45-7.58 (3 H), 7.75 (1 H), 7.85 (1 H); MS (EI) *m/z* 556, 538, 379, 353, 335, 301, 159, 142, 123, 109, 95.

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Scheme 35

Examples 220-224



Preparation 35-B: Scheme 35

To a cooled (0-5°C) mixture of Wang polystyrene resin 35-A (Advanced Chemtech, 2.0 g, ca. 1.5 mmol), N-Boc-4-iodo-L-phenylalanine (4.00 g, 10 mmol), and PPh₃ (1.30 g, 5.0 mmol) in THF (20 mL) was added diethyl azodicarboxylate (0.80 mL, 5.0 mmol) in 4 approximately equal portions at 5 min intervals. When the orange color had discharged the mixture was warmed to ambient temperature and stirred for 5 h. The mixture was diluted with THF (30 mL) and filtered. The resin was washed with DMF (5 x 50 mL), THF (5 x 50 mL), and MeOH (3 x 50 mL) and then dried in vacuo to afford the esterified resin 35-B (2.68 g) as a colorless powder: ¹³C NMR (100 MHz, CD₂Cl₂, 4mm MAS probe) δ 171.86, 155.33, 137.85, 136.40, 131.87, 128.00, 92.74, 80.09, 54.05, 38.05, 28.51.

Preparation 35-C-1: Scheme 35 where R³⁵ is 2,4,6-trichlorophenyl.

N₂ was bubbled through a mixture of N-Boc-4-iodo-L-phenylalanine functionalized Wang resin (35-B) (500 mg, ca. 0.3 mmol), PPh₃ (105 mg, 0.4 mmol), 2,4,6-trichloroaniline (490 mg, 2.5 mmol) and DIEA (1.74 mL, 10 mmol) in NMP (10 mL) for 10 min. Pd₂dba₃ (92 mg, 0.1 mmol) was added and the reaction mixture was placed under a CO atmosphere and heated (bath temp. 70 °C) for 18 h. Upon cooling to ambient temperature the mixture was diluted with 3% (w/v) sodium diethyldithiocarbamate in 95:5 NMP:DIEA (10 mL). After an additional 10 min the mixture was filtered and the resin washed with NMP (5 x 10 mL), THF (3 x 10 mL), and MeOH (3 x 10 mL) and dried in vacuo to afford 35-C-1 as a colorless powder.

Preparation 35-D-1: Scheme 35 where R³⁵ is 2,4,6-trichlorophenyl.

5 Resin 35-C-1 was swollen with methylene chloride (0.5 mL) and diluted with 95:5 TFA:H₂O (10 mL). After 90 min the mixture was filtered and the resin washed with TFA (3 x 5 mL), CH₂Cl₂ (3 x 5 mL) and MeOH (3 x 5 mL). The combined filtrates were concentrated in vacuo and the residue lyophilized from glacial acetic acid to provide the amino acid 35-D-1 (152 mg, 91%) as
10 a powder which was used without purification: MS (FAB) m/z (rel. intensity) 387 (M+H, 42), 427 (26), 426 (80), 389 (46), 387 (42), 366 (33), 279 (99), 177 (54), 146 (18), 119 (26), 23 (26); HRMS (FAB) calcd for C₁₆H₁₃Cl₃N₂O₃+H₁ 387.0070, found 387.0084.

15 Preparation 35-E-1: Scheme 35 where R³⁵ is 2,4,6-trichlorophenyl.

The amino acid 35-D-1 was dissolved in methanolic HCl (20 mL) and heated at 55°C for 18 h. Concentration in vacuo afforded the methyl ester
20 35-E-1 which was used without purification: MS (ES+) for C₁₇H₁₅Cl₃N₂O₃ m/z 400.9 (M+H)⁺.

Preparation 35-F-1: Scheme 35 where R³⁵ is 2,4,6-trichlorophenyl.

To a cooled (0-5°C) solution of the methyl ester
25 35-E-1, 15-D (97 mg, 0.38 mmol), and 1-hydroxy-7-azabenzotriazole (52 mg, 0.38 mmol) in CH₂Cl₂/DMF (1:2, 6 mL) was added EDC (73 mg, 0.38 mmol) followed by DIEA (0.23 mL, 1.14 mmol). The solution was gradually allowed to warm to ambient temperature and stirred an
30 additional 16 h. Volatiles were removed in vacuo and the residue partitioned between ethyl acetate and 0.25N aq. HCl. The organic layer was washed with saturated aq. NaHCO₃ and brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by
35 flash chromatography using ethyl acetate/CH₂Cl₂/hexane

(1:1:6) as eluant afforded 35-F-1 (115 mg) as an amorphous powder: ^1H NMR (300 MHz, CDCl_3) δ 7.96 (1 H), 7.86 (2 H), 7.20 (2 H), 5.86 (1 H), 4.92 (1 H), 3.72 (3 H), 3.17 (2 H), 2.49 (2 H), 2.10 (1 H), 1.69 (1 H), 1.41 (10 H), 1.25 (3 H), 1.19 (3 H), 0.76 (3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.90, 172.66, 171.88, 165.41, 140.88, 134.42, 133.50, 132.08, 131.27, 129.58, 128.44, 127.97, 80.25, 60.39, 56.64, 54.43, 52.91, 52.47, 46.38, 37.71, 32.33, 28.03, 22.99, 22.51, 21.93, 20.59, 14.17; MS (FAB) m/z (rel. intensity) 639 (M^+ , 17), 641 (17), 639 (17), 583 (16), 403 (27), 401 (28), 189 (23), 137 (18), 109 (99), 57 (59), 41 (20); HRMS (FAB) calcd for $\text{C}_{31}\text{H}_{37}\text{Cl}_3\text{N}_2\text{O}_6\text{H}$, 639.1795, found 639.1779.

15

Preparation of Example 220

(1*S*-*cis*)-N-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)-carbonyl]-4-[[[(1,1'-biphenyl)-4-yl]amino]-carbonyl]]-L-phenylalanine

Example 220 was prepared as described in Schemes 35 and 2 starting from 4-aminobiphenyl and 35-B: physical properties as follows: ^1H NMR (300 MHz, CD_3OD) δ 7.87 (1 H), 7.76 (2 H), 7.62 (4 H), 7.44 (4 H), 7.30 (1 H), 4.79 (1 H), 3.30 (1 H), 3.01 (1 H), 2.72 (1 H), 2.54 (1 H), 2.02 (1 H), 1.62 (1 H), 1.58 (1 H), 1.28 (3 H), 1.20 (3 H), 0.78 (3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 179.75, 175.49, 174.98, 168.82, 143.38, 142.03, 139.42, 138.75, 134.74, 130.70, 130.01, 128.86, 128.38, 128.31, 127.87, 122.68, 57.56, 54.69, 47.81, 38.43, 33.87, 23.94, 23.25, 22.57, 21.99; MS (FAB) m/z (rel. intensity) 543 (M^+ , 17), 109 (41), 83 (43), 81 (37), 71 (45), 69 (82), 67 (35), 57 (81), 55 (99), 43 (80); HRMS (EI) calcd for $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_6$ 542.2416, found 542.2429. Anal. Calcd for $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_6 \cdot 0.5 \text{H}_2\text{O}$: C, 69.67; H, 6.39; N, 5.08. Found: C, 69.72; H, 6.65; N, 4.75.

Preparation of Example 221

(1*S*-cis)-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(4-chlorophenyl)amino]-carbonyl]-L-phenylalanine

- 5 Example 221 was prepared as described in Schemes 35 and 2 starting from 4-chloroaniline and 35-B: physical properties as follows: ¹H NMR (300 MHz, CD₃OD) δ 7.85 (2 H), 7.68 (2 H), 7.40 (2 H), 7.36 (2 H), 4.82 (1 H), 3.29 (1 H), 3.05 (1 H), 2.81 (1 H), 2.54 (1 H), 1.96 (1 H), 1.70 (1 H), 1.24 (1 H), 0.91 (3 H), 0.86 (3 H), 0.77 (3 H); ¹³C NMR (75 MHz, CD₃OD) δ 179.74, 175.55, 174.65, 168.73, 143.39, 138.93, 134.55, 130.66, 130.55, 128.86, 123.68, 57.54, 54.62, 47.81, 38.33, 35.92, 33.86, 10 30.30, 29.00, 26.34, 23.21, 22.51, 21.98, 21.16; HRMS (FAB) calcd for C₂₆H₂₉ClN₂O₆+H₁ 501.1792, found 501.1790.

Preparation of Example 222

(1*S*-cis)-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)-carbonyl]-4-[[[(2-trifluoromethylphenyl)amino]-carbonyl]-L-phenylalanine

- 20 Example 222 was prepared as described in Schemes 35 and 2 starting from 2-(trifluoromethyl)aniline and 35-B. Physical properties as follows: ¹H NMR (300 MHz, CD₃OD) δ 7.86 (2 H), 7.66 (4 H), 7.40 (2 H), 4.78 (1 H), 3.30 (1 H), 3.10 (1 H), 2.72 (1 H), 2.49 (1 H), 1.98 (1 H), 1.62 (1 H), 1.48 (1 H), 1.28 (3 H), 1.20 (3 H), 0.78 (3 H); ¹³C NMR (75 MHz, CD₃OD) δ 179.70, 175.77, 173.54, 169.59, 143.34, 136.74, 124.18, 133.85, 131.74, 130.73, 128.89, 128.30, 25 127.13, 123.51, 57.56, 55.05, 62.54, 57.56, 55.05, 54.58, 50.06, 47.80, 38.21, 33.84, 23.89, 23.19, 22.52, 22.30, 21.85; IR (mull) 3302, 1708, 1656, 1613, 1592, 1530, 1508, 1320, 1294, 1260, 1206, 1173, 1123, 1059, 767 cm⁻¹; MS (FAB) m/z (rel. intensity) 535

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(M⁺, 99), 536 (32), 535 (99), 517 (25), 353 (46), 109 (57), 69 (14), 57 (13), 55 (14), 43 (13); HRMS (FAB) m/z calcd for C₂₇H₂₉F₃N₂O₆+H₁ 535.2056, found 535.2049. Anal. Calcd for C₂₇H₂₉F₃N₂O₆ · 0.5 H₂O: C, 59.66; H, 5.56; N, 5.15. Found: C, 59.75; H, 5.73; N, 4.72.

Preparation of Example 223

(1S-cis)-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,4,6-trichlorophenyl)amino]carbonyl]-L-phenylalanine

35-F-1 (110 mg, 0.16 mmol) was deprotected as described in Scheme 2 to afford example 223 (90 mg) as an amorphous powder: ¹H NMR (300 MHz, CD₃OD) δ 7.90 (2 H), 7.60 (1 H), 7.41 (2 H), 4.82 (1 H), 3.29 (1 H), 3.10 (1 H), 2.72 (1 H), 2.63 (1 H), 1.92 (1 H), 1.68 (1 H), 1.44 (1 H), 0.88 (6 H), 0.77 (3 H); ¹³C NMR (75 MHz, CD₃OD) δ 179.72, 175.52, 174.72, 168.90, 143.97, 136.86, 135.15, 133.59, 133.02, 130.82, 129.66, 129.09, 62.70, 57.53, 54.65, 38.41, 33.85, 23.91, 23.20, 22.53, 21.97; IR (mull) 3263, 3079, 1709, 1657, 1614, 1573, 1556, 1524, 1495, 1287, 1246, 1205, 1190, 869, 857 cm⁻¹; MS (ES⁺) for C₂₆H₂₇Cl₃N₂O₆ m/z 568.9 (M+H)⁺; Anal. Calcd for C₂₆H₂₇Cl₃N₂O₆: C, 54.80; H, 4.78; N, 4.92. Found: C, 55.00; H, 5.08; N, 4.64.

Preparation of Example 224

[1S-[1α(R*),3α]]-4-[[[(1-Carboxy-3-methylbutyl)-amino]carbonyl]-N-[(3-carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-L-phenylalanine

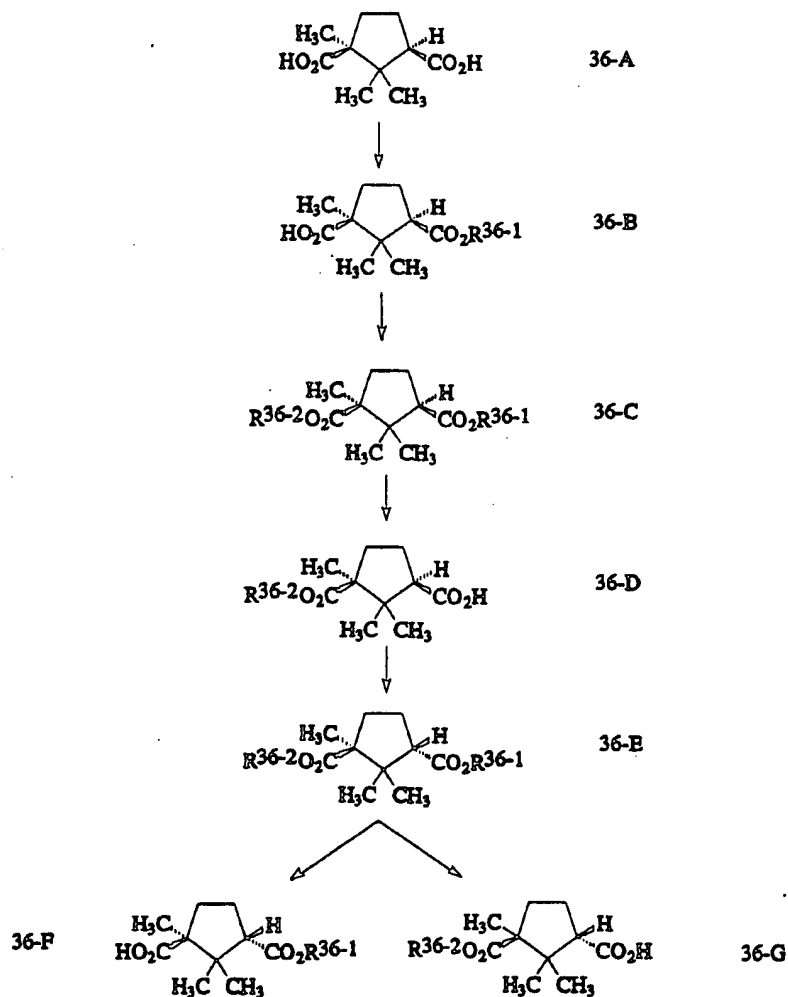
Example 224 was prepared as described in Schemes 35 and 2 starting from methyl L-leucinate and 35-B:

Physical properties as follows: ¹H NMR (300 MHz, CD₃OD) δ 7.78 (2 H), 7.34 (2 H), 4.87 (1 H), 4.72 (1 H), 3.30 (1 H), 3.02 (1 H), 2.82 (1 H), 2.68 (1 H), 1.98 (1 H), 1.74 (5 H), 1.23 (3 H), 0.97 (9 H),

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0.77 (3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 179.73, 176.33, 175.23, 174.66, 170.35, 143.05, 133.87, 130.52, 128.72, 62.41, 57.53, 54.63, 52.77, 47.79, 41.51, 38.30, 26.42, 23.90, 23.56, 23.18, 22.51, 21.93; MS (FAB) m/z (rel. intensity) 505 (M^+ , 99), 506 (27), 505 (99), 487 (20), 109 (29), 71 (20), 69 (34), 57 (34), 55 (33), 43 (36); HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_8 + \text{H}$, 505.2549, found 505.2570.

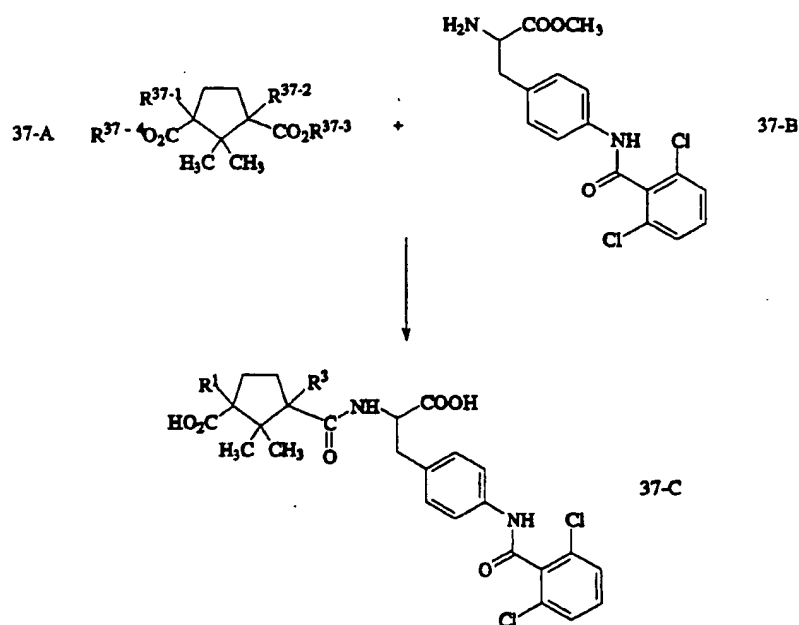
Scheme 36



Where R^{36-1} and R^{36-2} are independently defined as $-CH_3$, t -Bu, or $-CH_2C_6H_5$, and relative configuration is depicted by bold and dotted lines.

Scheme 36 teaches a general method (etherification, epimerization and ester deprotection) for the preparation of selectively protected camphoric acid isomers 36-B, 36-D, 36-G and 36-F.

Scheme 37



Where R^{37-1} and R^{37-2} are independently defined as $-H$ or $-CH_3$, and R^{37-3} and R^{37-4} are independently defined as $-H$, $-CH_3$, t -Bu, or $-CH_2C_6H_5$.

Scheme 37 teaches methods for the coupling of camphoric acid monoester isomers to isomers of 37-B and ester deprotection for the preparation of isomers of Example 54. 37-C-1 through 37-C-15.

Preparation of Example 237

Scheme 37: 37-C-1 where R³ is H, R¹ is CH₃, and the stereochemistry is (1S-cis) and D-Phenylalanine (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-D-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-1 was prepared as follows:

To a solution of (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-3-methyl diester (502.7 mg), 15-C, in methylene chloride (8 mL) at 0°C was added DIEA (1 mL), EDC (413.1 mg), HOBT (291.1 mg), and dimethylaminopyridine (26.4 mg). The reaction was stirred at 0°C for 15 minutes and then 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester, hydrochloride salt (803 mg), 37-B-2, was added and stirred at ambient temperature for 50 hours. The reaction was diluted with water and extracted with methylene chloride. The extracts concentrated in vacuo and the crude material purified by flash chromatography over silica gel. The crude material was applied to the column by concentrating it on a plug of silica gel and adding this plug to the top of the column. The column was eluted with methanol in methylene chloride to obtain (1S-cis)-N-[(3-[(1, 1-Dimethylethoxy)carbonyl]-2, 2, 3-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester (890 mg). Physical properties as follows: m.p. 265-270°C; ¹H NMR (CDCl₃) δ 7.63 (2 H), 7.35 (3 H), 7.19 (2 H), 4.84 (1 H), 3.76 (3 H), 3.18 (1 H), 3.01 (1 H), 2.61 (1 H), 2.47 (1 H), 2.06 (1 H), 1.74 (1 H), 1.44 (10 H), 1.14 (3 H), 1.03 (3 H), 0.66 (3 H); MS-ESI (m/z): 603 ([M-H]); MS-ESI (m/z): 605 ([M+H]). The deprotection of the carboxylic acids follows that of Examples 53, and 54 to obtain (1S-cis)-N-[(3-

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Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine. Physical properties as follows: m.p. 263-267°C; ¹H NMR(300MHz, DMSO-d₆). δ 10.6(1H), 7.83(1H), 7.52(5H), 7.2(2H), 4.45(1H), 3.1(1H), 2.82(1H), 2.62(1H), 2.3(1H), 1.94(1H), 1.55(1H), 1.3(1H), 1.05(3H), 0.83(3H), 0.45(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H]).

Preparation of Example 238

10 Scheme 37: 37-C-2 where R³ is H, R¹ is CH₃, and the stereochemistry is (1S-trans) and D-Phenylalanine (1S-trans)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-D-phenylalanine (C₂₆H₂₈Cl₂N₂O₆),
15 37-C-2 was prepared as follows:
The preparation follows that of Preparation 37-C-1. The starting materials are (1S-trans)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-ester, 36-G-1, and 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester,
20 hydrochloride salt, 37-B-2. Physical properties as follows: m.p. 158-168°C; ¹H NMR(300MHz, DMSO-d₆). δ 12.3(1H), 10.5(1H), 7.95(1H), 7.5(5H), 7.19(2H), 4.43(1H), 3.04(1H), 2.80(1H), 2.66(1H), 1.97(2H),
25 1.66(1H), 1.42(1H), 0.96(3H), 0.70(3H), 0.44(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H]).

Preparation of Example 239

Scheme 37: 37-C-3 where R³ is H, R¹ is CH₃, and the stereochemistry is (1S-trans) and L-Phenylalanine (1S-trans)-N-[(3-Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine (C₂₆H₂₈Cl₂N₂O₆),
30 37-C-3 was prepared as follows:

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The preparation follows that of Preparation 37-C-1. The starting materials are (1S-trans)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-ester, 36-G-1, and 4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester, hydrochloride salt, 37-B-1. Physical properties as follows: m.p. 172-178°C; ¹H NMR(300MHz, DMSO-d₆). δ 10.6(1H), 7.93(1H), 7.5(5H), 7.19(2H), 4.43(1H), 2.98(1H), 2.86(1H), 2.68(1H), 2.01(2H), 1.89(1H), 1.63(1H), 1.43(1H), 1.02(3H), 0.99(3H), 0.72(3H); MS-ESI (m/z): 533([M-H]).

Preparation of Example 240

Scheme 37: 37-C-4 where R³ is H, R¹ is CH₃, and the stereochemistry is (1R-trans) and L-Phenylalanine (1R-trans)-N-[(3-Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-4 was prepared as follows: The preparation follows that of Preparation 37-C-1. The starting materials are (1R-trans)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-ester, 36-G-2, and 4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester, hydrochloride salt, 37-B-1. Physical properties as follows: m.p. 168-170°C; ¹H NMR(300MHz, DMSO-d₆). δ 12.3(2H), 10.6(1H), 7.96(1H), 7.51(5H), 7.20(2H), 4.43(1H), 3.05(1H), 2.80(1H), 1.97(2H), 1.66(1H), 1.42(1H), 0.96(3H), 0.70(3H), 0.44(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H⁺]).

Preparation of Example 241

Scheme 37: 37-C-5 where R³ is H, R¹ is CH₃, and the stereochemistry is (1R-trans) and D-Phenylalanine

(1R-trans)-N-[(3-Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$), 37-C-5 was prepared as follows:

- 5 The preparation follows that of Preparation 37-C-1. The starting materials are (1R-trans)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-ester, 36-G-2, and 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester, hydrochloride salt, 37-B-2. Physical properties as follows: m.p. 158-165°C; 1H NMR(300MHz, DMSO- d_6). δ 10.6(1H), 7.93(1H), 7.51(5H), 7.19(2H), 4.43(1H), 2.98(1H), 2.86(1H), 2.68(1H), 2.02(1H), 1.88(1H), 1.62(1H), 1.43(1H), 1.02(3H), 0.99(3H), 0.73(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H⁺]).

Preparation of Example 242

- Scheme 37: 37-C-6 where R³ is H, R¹ is CH₃, and the stereochemistry is (1R-cis) and D-Phenylalanine (1R-cis)-N-[(3-Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$), 37-C-6 was prepared as follows:
- The preparation follows that of Preparation 37-C-1. The starting materials are (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-ester, 36-D, and 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester, hydrochloride salt, 37-B-2. Physical properties as follows: m.p. 166-170°C; 1H NMR(300MHz, DMSO- d_6). δ 10.65(1H), 7.81(1H), 7.51(5H), 7.20(2H), 4.44(1H), 2.99(1H), 2.85(1H), 2.68(1H), 2.34(1H), 1.88(1H), 1.52(1H), 1.30(1H), 1.15(3H), 1.10(3H), 0.65(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H⁺]).

Preparation of Example 243

Scheme 37: 37-C-7 where R³ is H, R¹ is CH₃, and the stereochemistry is (1R-cis) and L-Phenylalanine (1R-cis)-N-[(3-Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-7 was prepared as follows:
The preparation follows that of Preparation 37-C-1. The starting materials are (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-ester, 36-D, and 4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester, hydrochloride salt, 37-B-1. Physical properties as follows: m.p. 171-172°C; ¹H NMR(300MHz, DMSO-d₆). δ 10.6(1H), 7.82(1H), 7.51(5H), 7.18(2H), 4.45(1H), 3.1(1H), 2.82(1H), 2.62(1H), 2.32(1H), 1.93(1H), 1.58(1H), 1.34(1H), 1.06(3H), 0.83(3H), 0.45(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H⁺]).

Preparation of Example 244

Scheme 37: 37-C-8 where R³ is CH₃, R¹ is H, and the stereochemistry is (1S-cis) and L-Phenylalanine (1S-cis)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-8 was prepared as follows:
To a solution of (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 3-methyl ester, 36-B(501.3 mg) in DMF(5 mL) and DIEA(3 mL) was added O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate(1.0445 g) and the reaction stirred at ambient temperature for 1 hour. To the reaction was added 4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester, hydrochloride salt(1.0093 g), 37-B-1, and the reaction stirred for 3 days. The reaction was then diluted

with water and extracted with AcOEt. The concentrated extract was purified by flash chromatography on silica gel eluting with methanol in methylene chloride to obtain (1S-cis)-N-[(3-Methoxycarbonyl)-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester (2.272 g). A solution of LiOH (552 mg) in H₂O (20 mL) and 4 mL of 30% hydrogen peroxide was added to a solution of the above (1S-cis)-N-[(3-Methoxycarbonyl)-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester (C₂₈H₃₂Cl₂N₂O₆) (2.272 g) in 15 mL of methanol. The solution was stirred for 6 days. The methanol is then removed in vacuo. The aqueous layer is further diluted with water and extracted with diethyl ether and the extract discarded. The aqueous layer is acidified to pH = 3-4 with 0.6N HCl resulting in a precipitate. The precipitate is filtered washing with water to obtain (1S-cis)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine (1.1265 g). Physical properties as follows: m.p. 152-157°C. ¹H NMR (300MHz, DMSO-d₆). δ 12.3 (1H), 10.63 (1H), 7.50 (5H), 7.27 (1H), 7.18 (2H), 4.45 (1H), 2.99 (2H), 2.63 (1H), 2.25 (1H), 1.93 (1H), 1.69 (1H), 1.28 (1H), 1.16 (3H), 1.05 (3H), 0.50 (3H); MS-ESI (m/z): 533 ([M-H]); MS-ESI (m/z): 535 ([M+H⁺]).

Preparation of Example 245

Scheme 37: 37-C-9 where R³ is CH₃, R¹ is H, and the stereochemistry is (1S-cis) and D-Phenylalanine (1S-cis)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine (C₂₈H₂₈Cl₂N₂O₆), 37-C-9 was prepared as follows:

The preparation follows that of Preparation 37-C-8. The starting materials are (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 3-methyl ester, 36-B, and 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester, hydrochloride salt, 37-B-2. Physical properties as follows: m.p. 155-163°C; ¹H NMR(300MHz, DMSO-d₆). δ 12.3(1H), 10.6 (1H), 7.51(5H), 7.29(1H), 7.18(2H), 4.44(1H), 3.07(1H), 2.94(1H), 2.25(1H), 2.62(1H), 1.94(1H), 1.67(1H), 1.28(1H), 1.04(3H), 0.99(3H), 0.48(3H); MS-ESI (m/z): 533([M-H⁻]); MS-ESI (m/z): 535([M+H⁺]).

Preparation of Example 246

Scheme 37: 37-C-10 where R³ is CH₃, R¹ is H, and the stereochemistry is (1S-trans) and D-Phenylalanine (1S-trans)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-10 was prepared as follows: To a solution of (1S-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid, 36-F-1, (503.7 mg) in DMF(5 mL) and DIEA(3 mL) was added O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate(731.7 mg) and the reaction stirred at ambient temperature for 1 hour. To the reaction was added 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester, hydrochloride salt(698.6 mg), 37-B-2, and the reaction stirred for 5 days. The reaction was then diluted with water and extracted with AcOEt. The concentrated extract was purified by flash chromatography on silica gel eluting with methanol in methylene chloride to obtain (1S-trans)-N-[(3-(Phenylmethoxy)carbonyl)-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl

ester(1.1024 g). Physical properties as follows: ¹H NMR (CDCl₃) δ 7.82 (1 H), 7.58 (2 H), 7.28 (8 H), 7.05 (2 H), 6.07 (1 H), 5.06 (2 H), 4.74 (1 H), 3.66 (3 H), 3.07 (3 H), 2.05 (3 H), 1.53 (1 H), 1.21 (3 H), 0.90 (3 H), 0.75 (3 H); MS-ESI (m/z): 637([M-H⁻]); MS-ESI (m/z): 661([M+Na]⁺).

The product from above was dissolved in THF(10 mL) and 10% palladium on carbon(75 mg) was added and the mixture hydrogenated at atmospheric pressure for 26 hours. The reaction was then filtered and the filtrate concentrated to obtain (1S-trans)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester(896.3 mg). Physical properties as follows: MS-ESI (m/z): 547([M-H⁻]); MS-ESI (m/z): 571([M+Na]⁺). A solution of LiOH(213.2 mg) in H₂O(10 mL) and 2 mL of 30% hydrogen peroxide was added to a solution of (1S-trans)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester (896.3 mg) in 10 mL of methanol. The solution was stirred for 26 hours. The methanol is then removed in vacuo. The aqueous layer is further diluted with water and extracted with diethyl ether and the extract discarded. The aqueous layer is acidified to pH = 3-4 with 0.6N HCl resulting in a precipitate. The precipitate is filtered washing with water to obtain (1S-trans)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine(692.2 mg). Physical properties as follows: m.p. 145-150°C; ¹H NMR(300MHz, DMSO-d₆) δ 12.3(1H), 10.6 (1H), 7.51(5H), 7.29(1H), 7.18(2H), 4.44(1H), 3.07(1H), 2.94(1H), 2.25(1H), 2.62(1H), 1.94(1H), 1.67(1H), 1.28(1H), 1.04(3H), 0.99(3H), 0.48(3H); MS-ESI (m/z): 533([M-H⁻]); MS-ESI (m/z): 535([M+H⁺]).

Preparation of Example 247

Scheme 37: 37-C-11 where R^3 is CH_3 , R^1 is H, and the stereochemistry is (1S-trans) and L-Phenylalanine (1S-trans)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$), 37-C-11 was prepared as follows:
The preparation follows that of Preparation 37-C-10. The starting materials are (1S-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid, 36-F-1, and 4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester, hydrochloride salt, 37-B-1. Physical properties as follows: m.p. 145-153°C; 1H NMR(300MHz, DMSO- d_6). δ 12.3(1H), 10.6(1H), 7.51(5H), 7.29(1H), 7.18(2H), 4.42(1H), 3.01(2H), 2.70(1H), 1.88(2H), 1.73(1H), 1.36(1H), 1.04(3H), 0.94(3H), 0.78(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H $^+$]).

Preparation of Example 248

Scheme 37: 37-C-12 where R^3 is CH_3 , R^1 is H, and the stereochemistry is (1R-cis) and L-Phenylalanine (1R-cis)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$), 37-C-12 was prepared as follows:
The preparation follows that of Preparation 37-C-8. The starting materials are: (1R-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 3-methyl ester, 10-A, and 4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester, hydrochloride salt, 37-B-1. Physical properties as follows: m.p. 154-160°C. 1H NMR(300MHz, MeOH- d_4). δ 7.58(2H), 7.42(3H), 7.24(3H), 4.74(1H), 3.3(1H), 3.03(1H), 2.75(1H), 2.41(1H), 2.12(1H), 1.80(1H), 1.43(1H), 1.14(3H), 1.11(3H),

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0.63 (3H); MS-ESI (m/z): 533 ([M-H]); MS-ESI (m/z): 535 ([M+H]).

Preparation of Example 249

Scheme 37: 37-C-13 where R³ is CH₃, R¹ is H, and the stereochemistry is (1R-cis) and D-Phenylalanine (1R-cis)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-13 was prepared as follows:

10 The preparation follows that of Preparation 37-C-8. The starting materials are (1R-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 3-methyl ester, 10-A, and 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester, hydrochloride salt, 37-B-

15 2. Physical properties as follows: m.p. 155-159°C; ¹H NMR (300MHz, DMSO-d₆). δ 12.4 (1H), 10.6 (1H), 7.51 (5H), 7.19 (3H), 4.42 (1H), 2.99 (2H), 2.64 (1H), 2.26 (1H), 1.94 (1H), 1.68 (1H), 1.29 (1H), 1.17 (3H), 1.05 (3H), 0.51 (3H); MS-ESI (m/z): 533 ([M-H]).

20

Preparation of Example 250

Scheme 37: 37-C-14 where R³ is CH₃, R¹ is H, and the stereochemistry is (1R-trans) and L-Phenylalanine (1R-trans)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-14 was prepared as follows:

25 The preparation follows that of Preparation 37-C-10. The starting materials are (1R-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid, 36-F-2, and 4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester, hydrochloride salt, 37-B-1. . Physical

30 properties as follows: m.p. 148-155°C; ¹H NMR (300MHz,

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DMSO- d_6). δ 12.3(2H), 10.6 (1H), 7.53(5H), 7.27(1H), 7.21(2H), 4.38 2(1H), 3.03(2H), 2.73(1H), 1.92(2H), 1.79(1H), 1.43(1H), 1.04(3H), 0.75(3H), 0.71(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H⁺]).

5

Preparation of Example 251

Scheme 37: 37-C-15 where R³ is CH₃, R¹ is H, and the stereochemistry is (1R-trans) and D-Phenylalanine (1R-trans)-N-[(3-Carboxy-1, 2, 2-trimethylcyclopentyl)carbonyl]-4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine (C₂₆H₂₈Cl₂N₂O₆), 37-C-15 was prepared as follows:
The preparation follows that of Preparation 37-C-10. The starting materials are (1R-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid, 36-F-2, and 4-[(2, 6-dichlorobenzoyl)amino]-D-phenylalanine methyl ester, hydrochloride salt, 37-B-2. . Physical properties as follows: m.p.134-140°C; ¹H NMR(300MHz, DMSO- d_6). δ 12.3(1H), 10.6 (1H), 7.50(5H), 7.43(1H), 7.21(2H), 4.43(1H), 3.03(2H), 2.73(1H), 1.92(2H), 1.78(1H), 1.41(1H), 1.06(3H), 0.96(3H), 0.80(3H); MS-ESI (m/z): 533([M-H]); MS-ESI (m/z): 535([M+H⁺]).

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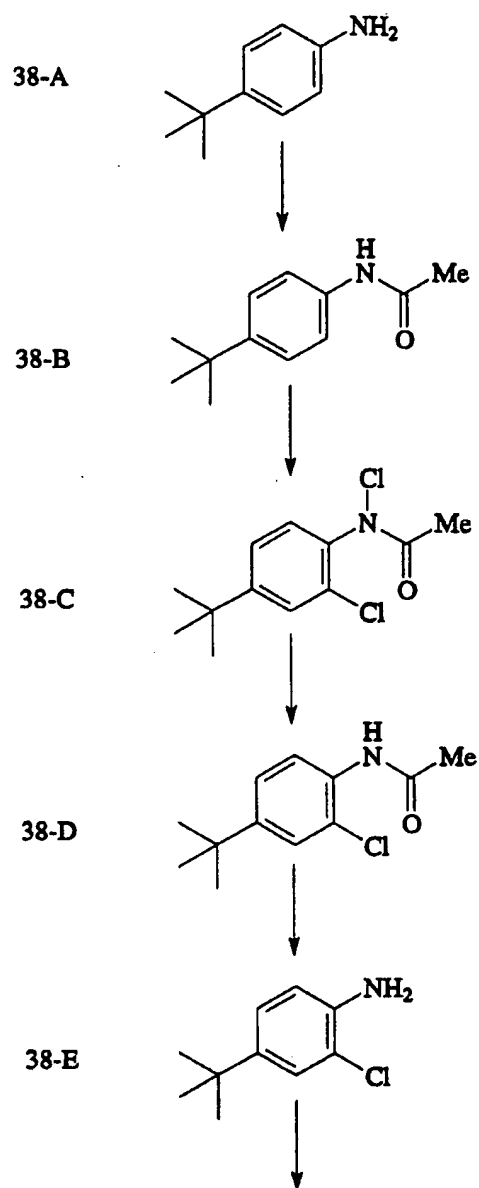
Preparation of Example 252

The synthesis for Example 252, (1S-cis)-N-[(3-Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-3-bromo-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine(C₂₆H₂₈Cl₂N₂O₆), is taught by Scheme 2 (Method B) as follows:
To a solution of (1R-cis)-1, 2, 2-Trimethylcyclopentane-1,3-dicarboxylic acid 1-(1, 1-dimethylethyl) ester(153.9 mg), 15-D, in methylene chloride(6 mL) at 0°C was added DIEA(1 mL), EDC(113.2 mg), HOBT(80.3 mg), and dimethylaminopyridine(20.1 mg). The reaction was stirred at 0°C for 20 minutes

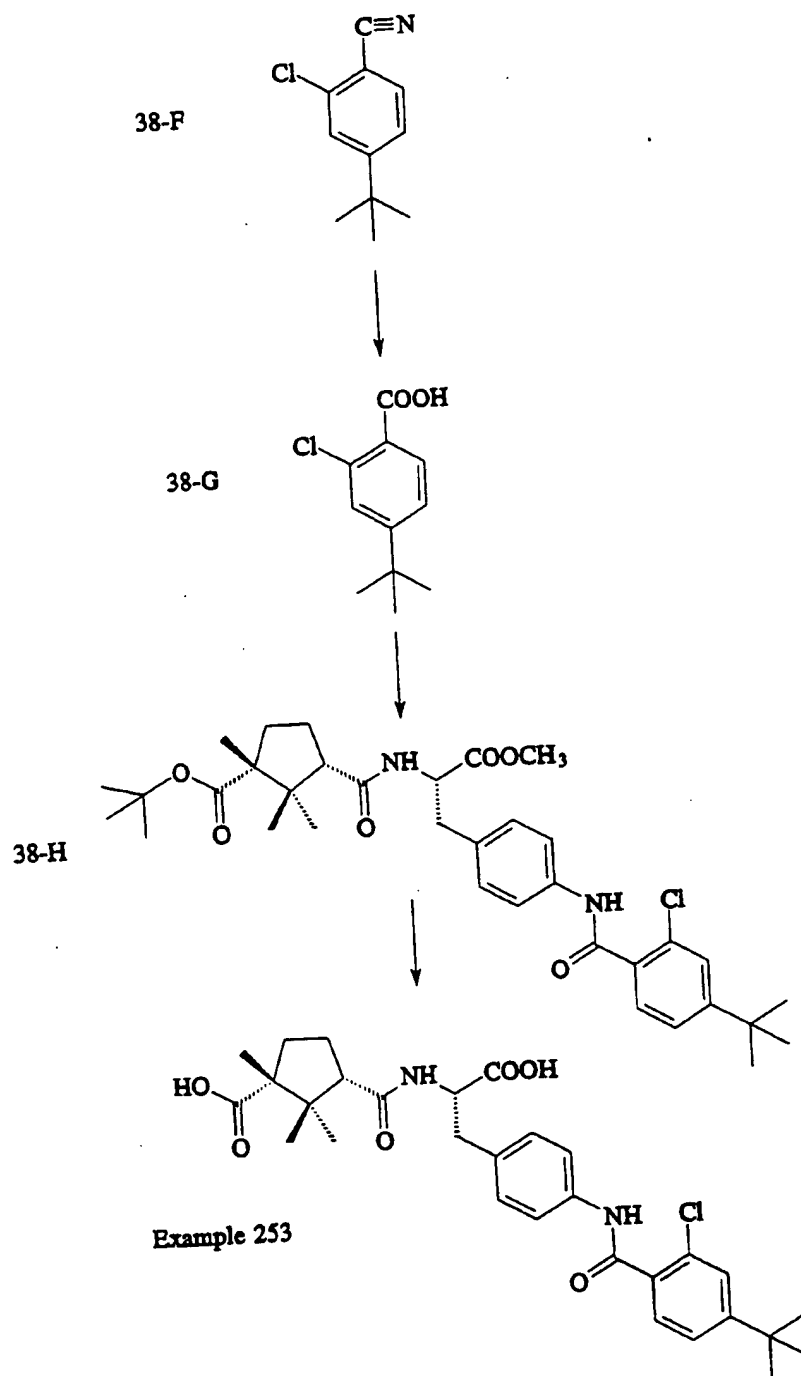
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- and then 3-Bromo-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester hydrochloride salt (259.4 mg) was added as a solution in methylene chloride (4 mL) and stirred at ambient temperature for 50 hours.
- 5 The reaction was diluted with water and extracted with methylene chloride. The extracts were washed with 0.5 N HCl, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography over silica gel eluting with AcOEt in
- 10 hexane to obtain (1S-cis)-N-[[3-[(1, 1-Dimethylethoxy)carbonyl]-2, 2, 3-trimethylcyclopentyl]carbonyl]-3-bromo-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester (153.8 mg). Physical properties as follows: ¹H
- 15 NMR (CDCl₃) δ 8.33 (1 H), 7.82 (1 H), 7.31 (4 H), 7.08 (1 H), 5.87 (1 H), 4.85 (1 H), 3.74 (3 H), 3.10 (2 H), 2.52 (2 H), 2.14 (1 H), 1.73 (1 H), 4.42 (10 H), 1.23 (3 H), 1.14 (3 H), 0.79 (3 H). MS-ESI (m/z): 681 ([M-H]); MS-ESI (m/z): 683 ([M+H⁺]).
- 20 The deprotection of the carboxylic acids follows that of Examples 53, and 54 to obtain (1S-cis)-N-[(3-Carboxy-2, 2, 3-trimethylcyclopentyl)carbonyl]-3-bromo-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine. Physical properties as follows: m.p. 150-152°C; ¹H
- 25 NMR (CD₃OD) δ 7.95 (1 H), 7.67 (1 H), 7.57 (1 H), 7.45 (3 H), 7.35 (1 H), 4.73 (1 H), 3.25 (1 H), 2.99 (1 H), 2.75 (1 H), 2.52 (1 H), 2.00 (1 H), 1.70 (1 H), 1.44 (1 H), 1.24 (3 H), 1.21 (3 H), 0.79 (3 H); MS-ESI (m/z): 611 ([M-H]); MS-ESI (m/z): 613 ([M+H⁺]).

Scheme 38 - Preparation of Example 253

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Preparation of Example 253

(1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichloro-4-[(1,1-dimethyl)ethyl]benzoyl)amino]-L-phenylalanine
5 (C₃₀H₃₇Cl₂N₂O₆).

4-[(1,1-Dimethyl)ethyl]acetanilide (C₁₂H₁₇NO, 38-B) To a solution of 4-tert-butylaniline 38-A (14.9 g, 99.8 mmol) and pyridine (11 mL, 0.14 mol) in CH₂Cl₂ (50 mL), under N₂ and at 0 °C, is added dropwise acetic
10 anhydride (12 mL, 0.13 mmol). The reaction mixture is stirred at rt for 20 h, and is then quenched with 0.5 M aqueous HCl (100 mL). The reaction mixture is extracted with CH₂Cl₂. The combined CH₂Cl₂ extracts are washed with 0.5 M NaOH and brine, and then are dried,
15 filtered and concentrated to give 38-B as an orange-colored solid (18.5 g). The solid is recrystallized from MeOH/Heptane to give a white solid (10.3 g, 54%): mp 172-173 °C; TLC (85:15 hexane/acetone) R_f = 0.19; ¹³C
NMR (CD₃OD) δ 171.48, 148.15, 137.19, 126.52, 121.03,
20 35.14, 31.81, 23.74; MS (-ESI) m/z 190.

N,2-Dichloro-4-[(1,1-dimethyl)ethyl]acetanilide (C₁₂H₁₅Cl₂NO, 38-C) To a suspension of 38-B (17.5 g, 91.5 mmol) and anhydrous NaOAc (19 g, 0.23 mmol) in HOAc (100 mL) under N₂ at 10 °C is added portionwise a
25 solution of Cl₂ (7g) in HOAc (100ml). Upon complete addition (approximately 15 min) the reaction mixture is allowed to warm to rt and is stirred for 1 h. A second portion of Cl₂ (approximately 8 g) in HOAc (100 mL) is added and the resulting mixture is stirred at
30 rt for 4.5 h. Finally, Cl₂ gas is bubbled directly into the stirred mixture for 30 min. This mixture is stirred at rt for 17 h. It is concentrated under reduced pressure, chasing the residual HOAc with two portions of toluene. The solid is dissolved in EtOAc.
35 The solution is filtered to give, after evaporation,

an orange-colored oil (24.7 g). The oil is purified by silica chromatography (90:10 heptane/EtOAc) to give an orange-colored oil (18.4 g) that is recrystallized from pentane to give 38-C as a white solid (12.8 g, 54%): mp 64-65 °C; TLC (90:10 heptane/EtOAc) R_f = 0.21; ^{13}C NMR (CDCl_3) δ 167.84, 155.65, 137.57, 133.57, 130.23, 127.91, 125.61, 35.11, 31.03, 21.52; MS (FAB) m/z 228, 226.

2-Chloro-4-[(1,1-dimethyl)ethyl]acetanilide ($\text{C}_{12}\text{H}_{16}\text{ClNO}$, 38-D). To a solution of 18.6 g (71.5 mmol) of 38-C in absolute EtOH (100 mL) is added 10 M NaOH (7.1 mL). An exothermic reaction ensues. After the temperature had moderated the mixture is heated at reflux for 1 h. The pH of the cooled mixture is adjusted to pH 7-8 with concentrated HCl. The resulting mixture is partially concentrated (to remove EtOH), and then is diluted with CH_2Cl_2 and brine. The CH_2Cl_2 layer is separated. The aqueous solution is extracted twice additionally with CH_2Cl_2 . The combined CH_2Cl_2 extracts are dried, filtered and concentrated to brown-colored oil. The oil is purified by silica chromatography (steps of 90:10 and 85:15 heptane/acetone) to give a solid (12.6 g), that is recrystallized from MeOH/pentane to give 38-D (7.49 g, 47%) as a white solid: mp 152-153 °C; TLC (85:15 heptane/acetone) R_f = 0.33; ^{13}C NMR (CDCl_3) δ 168.23, 148.25, 131.92, 125.89, 124.70, 122.59, 121.64, 34.49, 31.17, 24.70; MS (FAB) m/z 226.0995.

2-Chloro-4-[(1,1-dimethyl)ethyl]aniline ($\text{C}_{10}\text{H}_{14}\text{ClN}$, 38-E). To a suspension of 38-D (6.0 g, 26 mmol) in EtOH (90 mL) is added 10 N NaOH (10 mL). The resulting mixture is heated at reflux. The suspended solid dissolves gradually. After 17 h at reflux the solution is cooled to 0 °C and is neutralized to pH 7 with concentrated HCl. The mixture is concentrated partially (to remove

EtOH). the resulting aqueous mixture is diluted with brine, and is extracted with five portions of CH_2Cl_2 . The combined CH_2Cl_2 extracts are dried, filtered and concentrated to give 38-E as an orange-colored oil
5 (5.5 g): TLC (85:15 heptane/acetone) $R_f = 0.53$; ^1H NMR (CDCl_3) δ 7.25 (1H), 7.09 (1H), 6.72 (1H), 3.82 (2H), 1.27 (9H); MS (+ESI; MeOH) m/z 186, 184.

2-Chloro-4-[(1,1-dimethyl)ethyl]benzonitrile ($\text{C}_{11}\text{H}_{12}\text{ClN}$, 38-F). To a solution of aniline 38-E (5.5 g, 30 mmol)
10 in 10:6 HOAc/ H_2O (32 mL) is added concentrated H_2SO_4 (4.7 mL, 85 mmol). The brown-colored solution is cooled to 10 °C and is treated dropwise with a solution of NaNO_2 (2.3 g, 33 mmol) in H_2O (5 mL). After this addition is complete the reaction mixture is
15 stirred at 10°C for 1 h, yielding a yellow-colored solution. During this time a solution of KCN (9.8 g, 150 mmole) in H_2O (25 mL) is added to a cold (ice bath), mechanically stirred solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (9.0 g, 36 mmol) in H_2O (25 mL). To this mixture is added
20 NaHCO_3 (20 g, 0.24 mmol) and benzene (30 mL), and the entire mixture is heated to 50-55 °C to dissolve all of the solids. The this solution is added dropwise the solution of the diazonium salt over 20 min under N_2 and at 50-55°C. The reaction mixture is kept for 30 min at
25 50-55°C for 0.5 h after the addition. The mixture is cooled, and extracted thrice with benzene. The combined benzene extracts are washed with 1N NaOH and brine, and then dried, filtered and concentrated to give a reddish-brown oil (6.8 g). The oil is purified
30 by silica flash chromatography (steps of 95:5 and 90:10 heptane/ CH_2Cl_2) to give 38-F (2.4 g, 41%): TLC (75:25 heptane/ CH_2Cl_2) $R_f = 0.31$; ^1H NMR (CDCl_3) δ 7.58 (1H), 7.49 (1H), 7.37 (1H), 1.31 (9H); ^{13}C NMR (CDCl_3) δ 158.53, 136.59, 133.64, 127.22, 124.49, 116.29,
35 110.21, 35.49, 30.80.

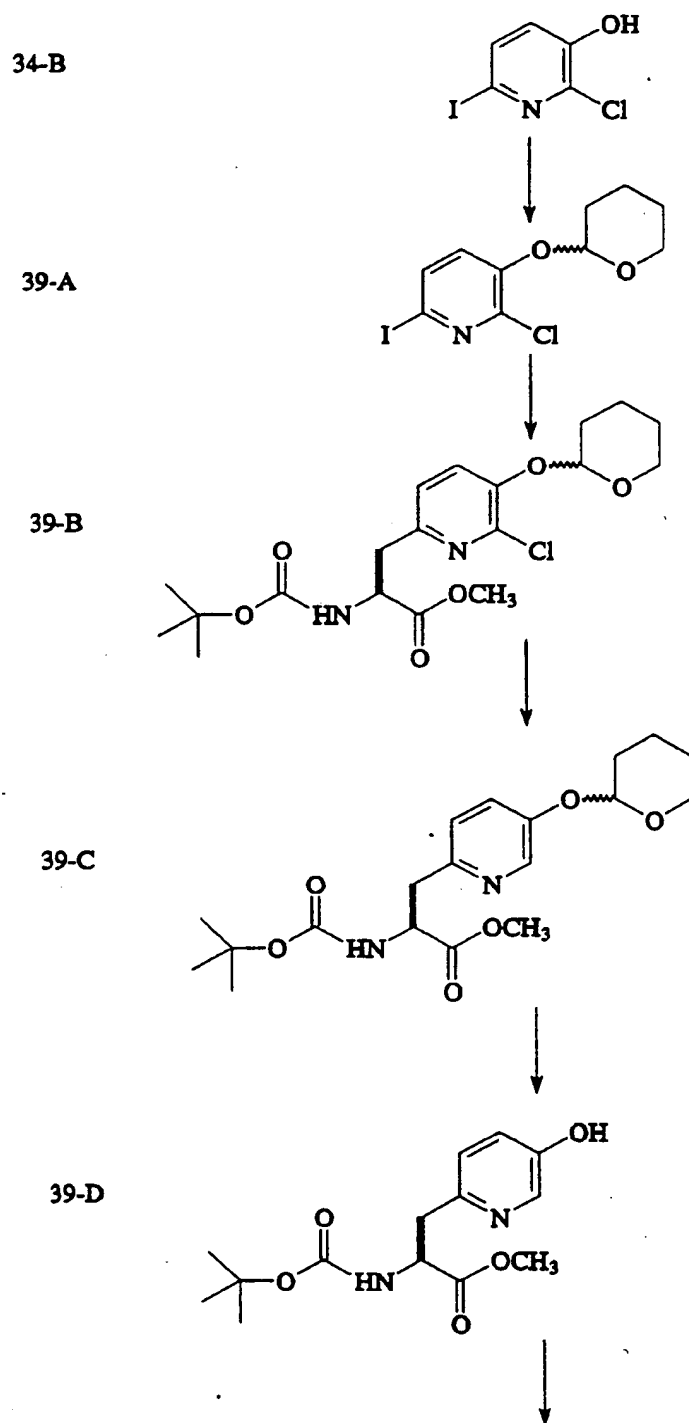
- 2-Chloro-4-[(1,1-dimethyl)ethyl]benzoic acid ($C_{11}H_{13}ClO_2$, 38-G). A solution of 38-F (2.28 g, 11.8 mmol), H_2O (7.4 mL), 10 N NaOH (5.9 mL), and 30 % H_2O_2 (6.7 mL) in EtOH (80 mL) is refluxed for 28 h. The solution is cooled to 0°C and neutralized to pH 7 with concentrated HCl. A solution of $NaHSO_3$ (7 g), dissolved in the minimal amount of H_2O , is added. The reaction mixture is concentrated partially (to remove most of the EtOH), basified to pH 12 with 1 N NaOH, and extracted twice with CH_2Cl_2 . The combined CH_2Cl_2 extracts are discarded. The aqueous solution is acidified with concentrated HCl to pH 3, and then is extracted with CH_2Cl_2 . The combined CH_2Cl_2 extracts are dried, filtered and concentrated to give 38-G (2.07 g, 83%) as a white crystalline solid: 1H NMR 11.62 (1H), 8.02 (1H), 7.51 (1H), 7.39 (1H), 1.36 (9H); ^{13}C NMR ($CDCl_3$) δ 171.17, 158.05, 134.84, 132.58, 128.75, 125.25, 123.96, 35.18, 30.91; MS (+ESI) m/z 237, 235 $[M+Na]^+$; MS (-ESI; MeOH) m/z 213, 211.
- (1*S*-cis)-N-[[3-(tert-Butoxycarbonyl)-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichloro-4-tert-butylbenzoyl)amino]-L-phenylalanine methyl ester ($C_{33}H_{47}Cl_2N_2O_6$, 38-H). A mixture of (1*S*-cis)-N-[[3-(tert-Butoxycarbonyl)-2,2,3-trimethylcyclopentyl]-carbonyl]-4-nitro-L-phenylalanine methyl ester (406 mg, 0.88 mmol) and 10% Pd/C (39 mg) in 1:1 MeOH:THF (10 mL) is hydrogenated (30 psi H_2) for 1 h. The reaction mixture is filtered and concentrated to give the aniline as a colorless oil. This aniline is coupled directly with acid 15-D (190 mg, 0.89 mmol), as described by the general procedure for the synthesis of intermediates 7-F, to give after silica flash chromatography (steps of 99:1, 98:2, and 98:3 $CHCl_3$ /Acetone) to give 38-H (224 mg, 41%): TLC (95:5 $CHCl_3$ /Acetone) R_f = 0.52; ^{13}C NMR ($CDCl_3$) δ 175.02, 172.53, 172.14, 164.53, 155.92, 136.86, 132.21, 131.96, 130.38, 130.31, 129.84,

127.48, 124.52, 120.26, 80.19, 56.69, 54.44, 53.11, 52.36, 46.39, 37.20, 35.03, 32.36, 31.00, 28.07, 22.98, 22.48, 21.98, 20.61; MS (FAB) m/z 627.3201.

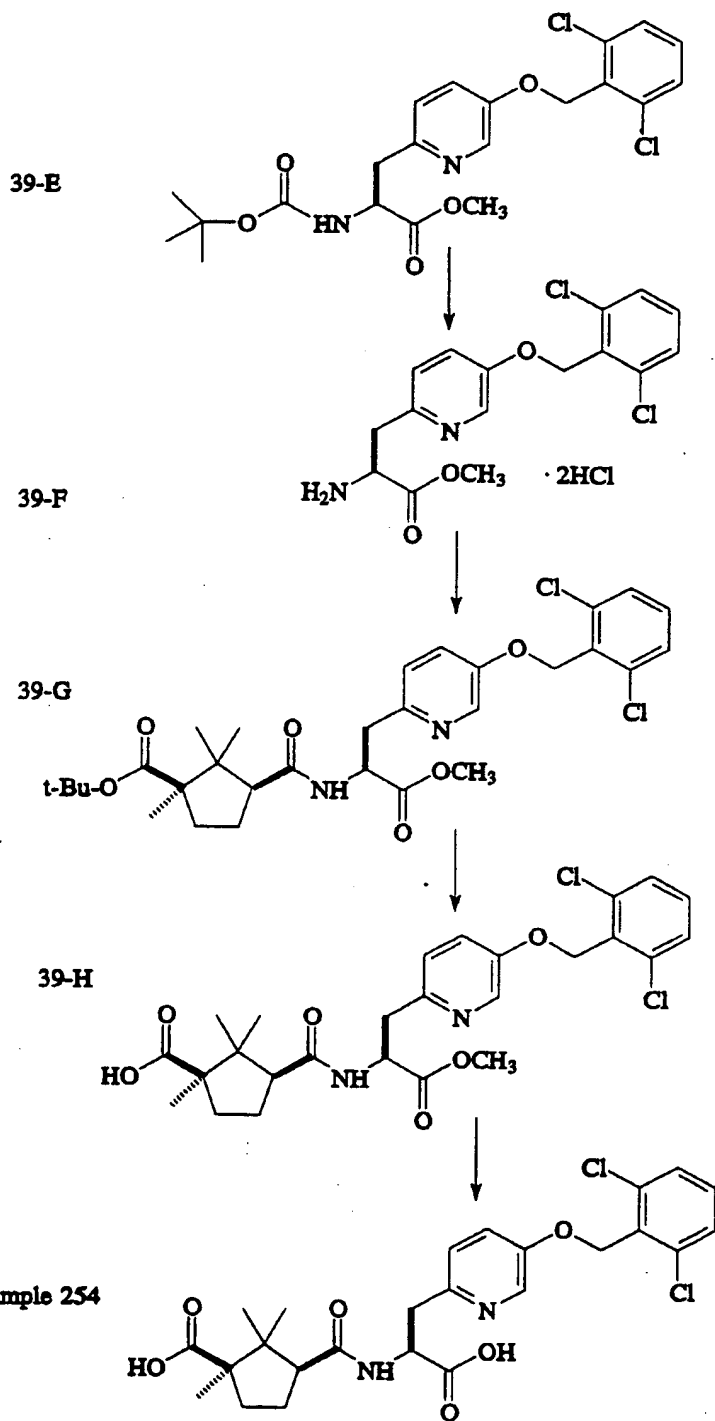
(1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichloro-4-[(1,1-dimethyl)ethyl]benzoyl)amino]-*L*-phenylalanine ($C_{39}H_{37}Cl_2N_2O_6$, Example 253). A solution of 38-H (101 mg, 0.16 mmol) in TFA (2 mL) is stirred at rt for 2 h. The solution is diluted with CH_2Cl_2 and concentrated thrice under reduced pressure. The residue is diluted with toluene and again concentrated under reduced pressure to an oil. The oil is dissolved in MeOH (1.0 mL) and then treated with H_2O (0.65 mL) and 1.00 M LiOH (0.35 mL). After 16 h a second portion of 1.00 M LiOH is added and the hydrolysis is allowed to proceed for an additional 4 h. The solution was diluted with H_2O and the pH adjusted to ca. 8-9. The neutralized solution is diluted with MeOH and then concentrated. The aqueous concentrate is diluted with additional H_2O , basified to pH 13 (1N NaOH), and extracted with Et_2O . The Et_2O extract is discarded. The aqueous phase is acidified to pH 2 (conc. HCl) and is extracted with EtOAc. The combined EtOAc extracts are dried, filtered and concentrated to give Example 253 (93 mg) as a colorless oil: 1H NMR (CD_3OD) δ 7.61 (2H), 7.55-7.44 (3H), 7.25 (2H), 4.69-4.78 (1H), 3.23 (1H), 3.00 (1H), 2.80-2.70 (1H), 2.60-2.46 (1H), 2.10-1.94 (1H), 1.78-1.61 (1H), 1.52-1.39 (1H), 1.36 (9H); 1.27 (3H), 1.23 (3H), 0.81 (3H); MS (-ESI) m/z 557, 555.

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Scheme 39



179



Preparation of Example 254

[1S-[1 α (R*),3 α]]- α -[[[3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-3-[(2,6-dichlorophenyl)methoxy]-6-pyridinepropanoic acid
5 (C₂₅H₂₈Cl₂N₂O₆).

(\pm)-2-Chloro-3-[(2-tetrahydropyranyl)oxy]-6-iodopyridine (C₁₀H₁₁ClINO₂, 39-A): To a solution of chloriodopyridinol 34-B (1.00 g, 3.91 mmol) and dihydropyran (1.0 mL, 10.6 mmol) in CH₂Cl₂ (10 mL) under
10 Ar at rt is added pyridinium chloride (0.050 g). The reaction mixture is stirred for 72 h. It is diluted with CH₂Cl₂, and is washed with satd aq NaHCO₃ and brine. The CH₂Cl₂ solution is dried, filtered and concentrated to an oil, that is purified by silica
15 flash chromatography (19:1 hexanes/EtOAc) to give 1.06 g (3.12 mmol, 80%) of 39-A: TLC (19:1 hexanes/EtOAc) R_f 0.24; ¹H NMR (CDCl₃, 300 MHz) δ 7.55 (1H), 7.17 (1H), 5.50 (1H), 3.77 (1H), 3.61 (1H), 2.07-1.57 (6H); MS (+ESI) m/z 361.9, 339.9.

(2S)-2-Chloro- α -[[[1,1-dimethylethoxy)carbonyl]amino]-3-[(2-tetrahydropyranyl)-oxy]-6-pyridinepropanoic acid methyl ester (C₁₉H₂₇ClN₂O₆, 39-B): To an amberized flask containing Reference Example 57 (1.81 g, 5.52 mmol) and activated Zn dust (0.349 g, 5.51 mmol) under Ar is
25 added THF (2 mL) and 1,2-dibromoethane (0.018 mL, 0.21 mmol). The suspension is brought to reflux for several minutes, cooled to approximately 30 °C, and TMSCl (0.17 mL of a 1 M solution in THF) is added. The reaction mixture is stirred at 40 \pm 5 °C for 30 min,
30 cooled in an ice bath, and solid PdCl₂(PPh₃)₂ (0.192 g) is added. A degassed solution of the iodide 39-A (0.936 g, 2.76 mmol) in 1:1 THF/dimethylacetamide (5.6 mL) is added. This reaction mixture is stirred for 4 h at 45 \pm 5 °C. It is then cooled to 0 °C, quenched with
35 satd aq NH₄Cl, and extracted with EtOAc. The combined

- EtOAc portions are washed with satd aq NH_4Cl and brine, and are dried, filtered and concentrated to a green-yellow colored foam. This foam is purified by silica flash chromatography (7:3 hexanes/EtOAc) to give 0.879 g (1.85 mmol, 60%) of 39-B: TLC (7:3 hexanes/EtOAc) R_f 0.21; ^1H NMR (CDCl_3 , 300 MHz) δ 7.39 (1H), 7.00 (1H), 5.46 (1H), 4.61 (1H), 4.13 (1H), 3.80 (3H), 3.62 (1H), 3.20 (1H), 2.13-1.53 (6H), 1.42 (9H); MS (+ESI) m/z 474.0.
- 10 (S)- α -[[(1,1-Dimethylethoxy)carbonyl]amino]-3-[(2-tetrahydropyranyl)oxy]-6-pyridinopropanoic acid methyl ester ($\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_6$, 39-C): A suspension of pre-reduced Pd/CaCO₃ (3.5 g) and 39-B (1.15 g, 2.77 mmol) in EtOH (40 mL) is hydrogenated (30 psi H_2) for 19 h at rt. The mixture is filtered, and the filtrate is evaporated to give a yellow-colored foam that is purified by silica flash chromatography (600:400:1 hexanes/EtOAc/iPrOH) to give 0.367 g (0.96 mmol, 35%) of 39-C: TLC (1:1 hexanes/EtOAc) R_f 0.27; ^1H NMR (CDCl_3 , 300 MHz) δ 8.30 (1H), 7.29 (1H), 7.03 (1H), 5.81 (1H), 5.39 (1H), 4.65 (1H), 3.86 (1H), 3.73 (3H), 3.62 (1H), 3.21 (2H), 1.96-1.53 (6H), 1.42 (9H); MS (+ESI) m/z 381.1.
- 25 (S)- α -[[(1,1-Dimethylethoxy)carbonyl]amino]-5-hydroxy-2-pyridinopropanoic acid methyl ester ($\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_5$, 39-D): A solution of 39-C (0.346 g, 0.91 mmol) and pyridinium p-toluenesulfonate (0.031 g, 0.12 mmol) in EtOH (8 mL) is stirred at 55 ± 5 °C for 20 h. The reaction mixture is cooled to rt, and concentrated in vacuo. The residue is taken up in EtOAc (150 mL). This solution is washed with brine, dried, filtered and concentrated to a pale yellow-colored oil that is purified by silica flash chromatography (500:500:1 hexanes/EtOAc/iPrOH). Evaporation of the column fractions gives recovered 39-C (0.27 mmol) and 0.132 g (0.45 mmol, 49%) of 39-D: TLC (1:1 hexanes/EtOAc) R_f

0.18; ¹H NMR (CDCl₃, 300 MHz) δ_{8.13} (1H), 7.13 (1H), 7.03 (1H), 5.71 (1H), 4.65 (1H), 3.70 (3H), 3.20 (2H), 1.39 (9H); MS (+ESI) m/z 297.1.

(S)-5-[(2,6-Dichlorophenyl)methoxy]-α-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-pyridinepropanoic acid methyl ester (C₂₁H₂₄Cl₂N₂O₅, 39-E): To a solution of 39-D (0.126 g, 0.43 mmol), 2,6-dichlorobenzylalcohol (0.075 g, 0.43 mmol) and PPh₃ (0.113 g, 0.43 mmol) in dry THF (4 mL) at 0 °C under Ar is added DEAD (0.068 mL). The reaction mixture is permitted to warm to rt, and is stirred for 18 h. It is concentrated. The residue is purified by silica flash chromatography (700:300:1 hexanes/EtOAc/iPrOH) to give 0.149 g (0.33 mmol, 76%) of 39-E: TLC (7:3 hexanes/EtOAc) R_f 0.34; ¹H NMR (CDCl₃, 300 MHz) δ_{8.31} (1H), 7.37 (2H), 7.25 (2H), 7.08 (1H), 5.81 (1H), 5.29 (2H), 4.65 (1H), 3.70 (3H), 3.24 (2H), 1.63 (1 H), 1.43 (9H); ¹³C NMR (CDCl₃, 75 MHz) δ_{172.47}, 155.50, 153.82, 149.71, 137.33, 137.00, 131.51, 130.72, 128.56, 123.99, 122.78, 79.74, 65.64, 53.25, 52.27, 38.43, 28.33; MS (+ESI) m/z 454.9.

(S)-α-Amino-5-[(2,6-dichlorophenyl)methoxy]-2-pyridinepropanoic acid methyl ester dihydrogen chloride salt (C₁₆H₁₆Cl₂N₂O₃·2HCl, 39-F): A solution of carbamate 39-E (0.546 g, 1.20 mmol) in 4 M HCl in dioxane (12 mL) is stirred at rt under Ar for 16 h. The reaction mixture is concentrated in vacuo. The residue is dissolved in H₂O (40 mL), and this solution is extracted with Et₂O. The aqueous solution is frozen and lyophilized to give 0.485 g (1.13 mmol, 94%) of 39-F as a light yellow-colored solid: ¹H NMR (CD₃SOCD₃, 300 MHz) δ_{8.75} (3H), 8.47 (1H), 7.81 (1H), 7.57 (3H), 7.48 (1H), 5.35 (2H), 4.49 (1H), 3.67 (3H), 3.42 (2H); ¹³C NMR (CD₃SOCD₃, 75 MHz) δ_{169.42}, 154.95, 146.54, 136.57, 134.35, 132.50, 131.30, 129.36, 126.72, 126.52, 66.40, 53.32, 51.79, 34.81.

[1S-[1 α (R*),3 α]]-3-[(2,6-Dichlorophenyl)methoxy]- α -
 [[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-
 trimethylcyclopentyl]carbonyl]amino]-6-
 pyridinepropanoic acid methyl ester (C₂₃H₃₀Cl₂N₂O₆, 39-G):

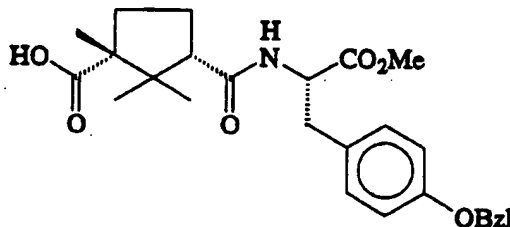
- 5 To a mixture of 15-D (0.141 g, 0.55 mmol), EDC (0.108 g, 0.57 mmol), HOBT (0.079 g, 0.58 mmol), DMAP (0.020 g, 0.16 mmol) and amine 39-F (0.246 g, 0.57 mmol) in CH₂Cl₂ (6 mL) at 0 °C under Ar is added Et₃N (0.18 mL, 1.26 mmol). The yellow-colored reaction mixture is
 10 stirred at rt for 90 h. It is diluted with CH₂Cl₂, and washed with H₂O, 0.5 M aq HCl, H₂O, satd aq NaHCO₃, and H₂O. The CH₂Cl₂ solution is dried, filtered and concentrated to a pale yellow-colored foam, that is purified by silica flash chromatography (600:400:1
 15 hexanes/EtOAc.iPrOH) to give 0.195 g (0.33 mmol, 60%) of 39-G: TLC (3:2 hexanes/EtOAc) R_f 0.49; ¹H NMR (CDCl₃, 300 MHz) δ 8.28 (1H), 7.40-7.28 (4H), 7.13 (1H), 5.31 (2H), 4.92 (1H), 3.68 (3H), 3.33 (1H), 3.25 (1H), 2.65 (1H), 2.53 (1H), 2.21 (1H), 1.67 (1H), 1.44 (9H), 1.31
 20 (3H), 1.18 (3H), 0.83 (3H).

- [1S-[1 α (R*),3 α]]- α -[[3-Carboxy-2,2,3-
 trimethylcyclopentyl]carbonyl]amino]-3-[(2,6-
 dichlorophenyl)methoxy]-6-pyridinepropanoic acid
 methyl ester (C₂₃H₃₀Cl₂N₂O₆, 39-H): A solution of diester
 25 39-G (0.195 g, 0.33 mmol) in TFA (4 mL) under Ar is stirred at 0 °C for 1 h and at rt for 2 h. The solution is concentrated, azeotroped thrice from toluene, and dried under vacuum to give 39-H as a yellow-colored glass: TLC (400:600:5
 30 hexanes/EtOAc/HCO₂H) R_f 0.29; ¹H NMR (CDCl₃, 300 MHz) δ 8.46 (1H), 7.87 (1H), 7.74 (1H), 7.51 (1H), 7.42-7.26 (2H), 5.42 (2H), 5.01 (1H), 3.80 (3H), 3.62 (1H), 3.45 (1H), 2.70 (1H), 2.48 (1H), 1.97 (1H), 1.65 (1H), 1.49 (1H), 1.28 (3H), 1.24 (3H), 0.76 (3H).

[1S-[1 α (R*),3 α]]- α -[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-3-[(2,6-dichlorophenyl)methoxy]-6-pyridinepropanoic acid (C₂₅H₂₈Cl₂N₂O₆, Example 254): A solution of 39-H (0.33 mmol) and LiOH·H₂O (0.068 g, 1.62 mmol) in 2:1 THF/H₂O (10.5 mL) is stirred under Ar for 5 h at rt. The reaction mixture is diluted with cold H₂O, acidified with aq 1 M HCl, and extracted with EtOAc. The combined EtOAc extracts are washed with brine, and are dried, filtered and concentrated to a pale yellow-colored foam that is purified by silica flash chromatography (600:400:2 hexanes/EtOAc/HCO₂H). The purified product is azeotroped thrice from toluene to remove HCO₂H. It is dissolved in MeCN (10 mL) and the solution is diluted with H₂O (10 mL). The solution is frozen and lyophilized to give, as a beige-colored solid, 0.170 g (0.32 mmol, 98%) of Example 254: mp 118-122 °C; TLC (150:50:1 EtOAc/hexanes/HCO₂H) R_f 0.41; ¹H NMR (CD₃SOCD₃, 300 MHz) δ 8.43 (1H), 7.86 (2H), 7.58-7.47 (3H), 7.32 (1H), 5.28 (2H), 4.64 (1H), 3.24-2.99 (2H), 2.61 (1H), 2.32 (1H), 1.83 (1H), 1.51 (1H), 1.30 (1H), 1.12 (3H), 1.09 (3H), 0.63 (3H).

EXAMPLES

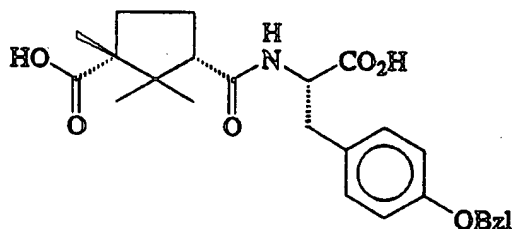
Example 1: (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-(phenylmethyl)-L-tyrosine methyl ester (C₂₇H₃₃NO₆).



DIEA (0.65 g) was added dropwise to a mixture of (1R)-camphoric anhydride (0.18 g) and O-benzyl-L-

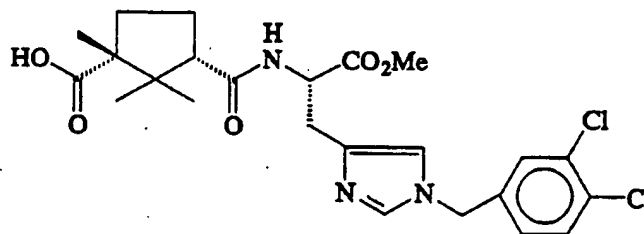
tyrosine methyl ester hydrochloride (0.33 g) in DMF (2 ml) at 0°C. The mixture was stirred at 40°C for 15 hr, cooled, diluted with AcOEt, and acidified with 1N HCl to pH 5. The organic layer was washed with H₂O, brine, dried over Na₂SO₄, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent; 98:2, CHCl₃/MeOH) to give (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine methyl ester (C₂₇H₃₃NO₆) (0.45 g) as a gum. MS (m/z): 468 (MH⁺).

Example 2. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine (C₂₆H₃₁NO₆).



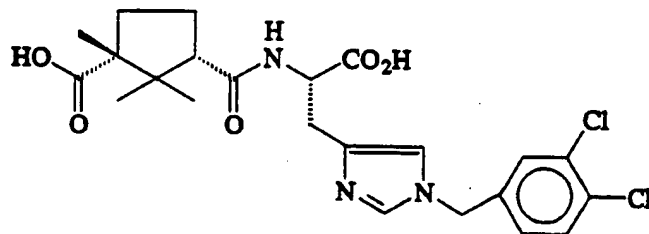
LiOH (72 mg) was added to a mixture of (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine methyl ester (C₂₇H₃₃NO₆) (403 mg), THF (3 ml), and H₂O (3 ml). The mixture was stirred at room temperature for 4 hr, acidified with 1N HCl, and extracted with AcOEt. The extract was dried over Na₂SO₄ and the solvent was removed in vacuo to give (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine (391 mg), mp 146-149°C, MS (m/z): 452 ([M-H]⁻).

Example 3. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-1-[(3,4-dichlorophenyl)methyl]-*L*-histidine methyl ester ($C_{24}H_{29}Cl_2N_3O_5$).



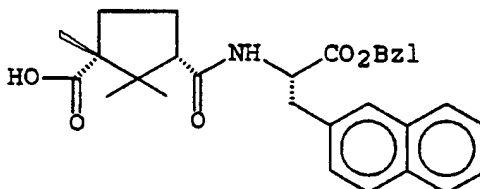
5 DIEA (4.48 g) was added to a mixture of 1-(3,4-dichlorobenzyl)-*L*-histidine methyl ester (5.56 g) and (1*R*)-camphoric anhydride (2.53 g) in DMF (50 ml). The mixture was stirred at 40°C for 17 hr, cooled, diluted with H_2O , acidified with 5% HCl to pH 5, and extracted
 10 with $CHCl_3$. The extract was washed with H_2O , brine, and dried over $NaSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (eluent: 100:1, $CHCl_3$ /MeOH), followed by recrystallization from AcOEt/MeOH to give (1*S*-*cis*)-*N*-
 15 [(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-1-[(3,4-dichlorophenyl)methyl]-*L*-histidine methyl ester (5.90 g), mp 174-175°C (dec), MS (m/z): 510 (MH^+).

Example 4. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-1-[(3,4-dichlorophenyl)methyl]-*L*-histidine
 20 ($C_{23}H_{27}Cl_2N_3O_5$).



1N NaOH (7.3 ml) was added dropwise to a mixture of (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-1-[(3,4-dichlorophenyl)methyl]-*L*-histidine methyl ester ($C_{24}H_{29}Cl_2N_3O_5$) (1.50 g) in MeOH (20 ml) at 0°C. The mixture was stirred at room temperature for 15 hr, concentrated in vacuo, diluted with H_2O , and acidified with 1N HCl to pH 5-6. The resulting precipitate was collected by filtration, washed with H_2O , dried, and recrystallized from DMF/ H_2O to give (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-1-[(3,4-dichlorophenyl)methyl]-*L*-histidine (0.87 g), mp 148-149°C (dec), MS (m/z):496 (MH^+).

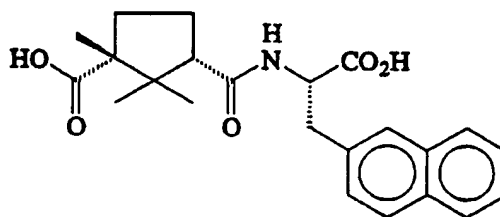
Example 5. [1*S*-[1 α (*R**),3 α]]- α -[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-2-naphthalenepropanoic acid phenylmethyl ester ($C_{30}H_{33}NO_5$).



Benzyl (S)-2-amino-3-(2-naphthyl) propionate tosylate (0.20 g) was partitioned between AcOH and sat. $NaHCO_3$. The organic layer was washed with H_2O , brine, dried over Na_2SO_4 , and the solvent was removed in vacuo. DMF (5 ml) and (1*R*)-camphoric anhydride (0.20 g) were added to the residue. The mixture was stirred at 30-40°C for 17 hr, cooled, and poured into H_2O . The resulting mixture was extracted with AcOH. The extract was washed with H_2O , brine, dried over Na_2SO_4 , and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel

(eluent; 9:1, $\text{CHCl}_3/\text{AcOEt}$) to give [1S-[1 α (R*),3 α]]- α -
 [[(3-Carboxy-2,2,3-
 trimethylcyclopentyl)carbonyl]amino]-2-
 naphthalenepropanoic acid phenylmethyl ester (0.51 g)
 5 as an oil. MS (m/z): 488 (MH^+).

Example 6. [1S-[1 α (R*),3 α]]- α -[[(3-Carboxy-2,2,3-
 trimethylcyclopentyl)carbonyl]amino]-2-
 naphthalenepropanoic acid ($\text{C}_{23}\text{H}_{27}\text{NO}_5$).

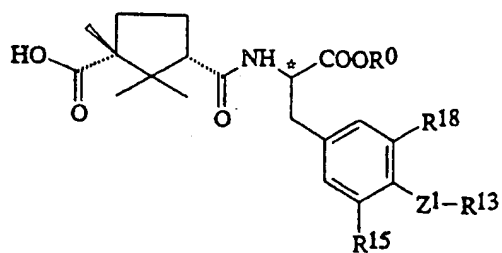


10 10% Pd-C (0.05 g) was added to a solution of
 [1S-[1 α (R*),3 α]]- α -[[(3-Carboxy-2,2,3-
 trimethylcyclopentyl)carbonyl]amino]-2-
 naphthalenepropanoic acid phenylmethyl ester ($\text{C}_{30}\text{H}_{33}\text{NO}_5$)
 (0.20g) in MeOH (10ml) and the mixture was subjected
 to hydrogenolysis at a hydrogen pressure of 50 psi.
 15 The catalyst was filtered off and the filtrate was
 evaporated in vacuo to give [1S-[1 α (R*),3 α]]- α -[[(3-
 Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-2-
 naphthalenepropanoic acid (0.18 g), MS (m/z): 398
 (MH^+).

20 Examples 7 through 51 were prepared in a similar
 manner as described in Examples 1-6, and are shown in
 Tables 1, 2, and 3.

Table 1

Examples 7 through 20:



(* : R- or S- form)


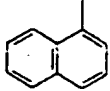
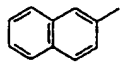
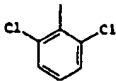
Ex. No.	*	R ⁰	R ¹⁵	Z ¹	R ¹³	R ¹⁸	physicochemical property
7	S	H	H	single bond	t-BuO-	H	M.P.: 98-100°C MS (m/z) : 420 (MH ⁺)
8	S	CH ₃	H	-OCH ₂ -		H	gum MS (m/z) : 518 (MH ⁺)
9	S	H	H	-OCH ₂ -		H	M.P.: 92-93°C MS (m/z) : 502 ([M-H] ⁻)
10	S	H	H	-OCH ₂ -		H	MS (m/z) : 504 (MH ⁺)
11	S	CH ₃	H	-OCH ₂ -		H	gum MS (m/z) : 536 (MH ⁺)

Table 1 (continued) 190

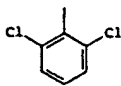
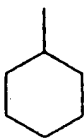
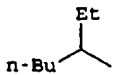
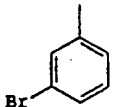
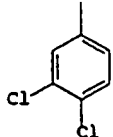
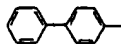
Ex. No.	*	R ⁰	R ¹⁵	Z ¹	R ¹³	R ¹⁸	physicochemical property
12	S	H	H	-OCH ₂ -		H	M.P.: 95-97°C MS (m/z): 520 ([M-H] ⁺)
13	S	H	H	-OCH ₂ -		H	M.P.: 102-105°C MS (m/z): 460 (MH ⁺)
14	S	H	H	-OCH ₂ -		H	M.P.: 94-97°C MS (m/z): 476 (MH ⁺)
15	S	H	I	-OCH ₂ -		I	M.P.: 210-212°C (dec.) MS (m/z): 784, 786 (MH ⁺)
16	S	H	H	-OCH ₂ -		H	MS (m/z): 520 ([M-H] ⁺)
17	S	H	PhCH ₂ O	-OCH ₂ -	Ph	H	MS (m/z): 558 ([M-H] ⁺)

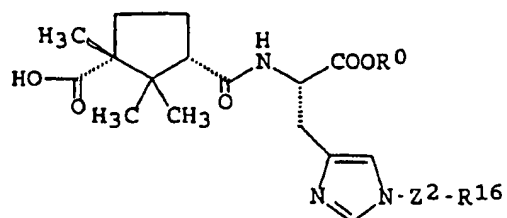
Table 1 (continued) 191

Ex. No.	*	R ⁰	R ¹⁵	Z ¹	R ¹³	R ¹⁸	physicochemical property
18	S	H	H	-OCH ₂ -		H	MS (m/z) : 530 (MH ⁺)
19	R	CH ₃	H	-OCH ₂ -	Ph	H	gum MS (m/z) : 468 (MH ⁺)
20	R	H	H	-OCH ₂ -	Ph	H	MS (m/z) : 454 (MH ⁺)

192

Table 2

Examples 21 through 38:



Ex. No.	R ⁰	Z ¹	R ¹⁶	physicochemical property
21	CH ₃	single bond	-C(Ph) ₃	gum MS (m/z) : 594 (MH ⁺)
22	H	single bond	-C(Ph) ₃	MS (m/z) : 580 (MH ⁺)
23	CH ₃	CH ₂		gum MS (m/z) : 510 (MH ⁺)
24	H	CH ₂		MS (m/z) : 496 (MH ⁺)

Table 2 (con't)

193

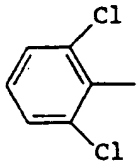
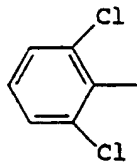
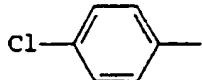
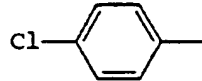
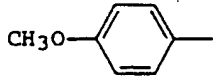
Ex. No.	R ⁰	Z ²	R ¹⁶	physicochemical property
25	CH ₃	CH ₂		gum MS (m/z) : 510 (MH ⁺)
26	H	CH ₂		MS (m/z) : 496 (MH ⁺)
27	CH ₃	CH ₂		gum MS (m/z) : 476 (MH ⁺)
28	H	CH ₂		MS (m/z) : 462 (MH ⁺)
29	H	CH ₂	Ph	M.P. : 258-259°C (dec.) MS (m/z) : 428 (MH ⁺)
30	CH ₃	CH ₂		gum MS (m/z) : 472 (MH ⁺)

Table 2 (con't)

194

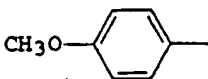
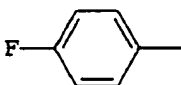
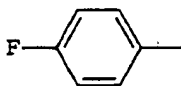
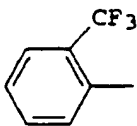
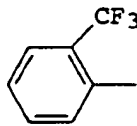
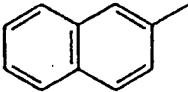
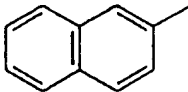
Ex. No.	R ⁰	Z ²	R ¹⁶	physicochemical property
31	H	CH ₂		MS (m/z) : 458 (MH ⁺)
32	H	CH ₂	PhCH ₂ O	MS (m/z) : 458 (MH ⁺)
33	CH ₃	CH ₂		^{gum} MS (m/z) : 460 (MH ⁺)
34	H	CH ₂		MS (m/z) : 446 (MH ⁺)
35	CH ₃	CH ₂		^{gum} MS (m/z) : 510 (MH ⁺)
36	H	CH ₂		MS (m/z) : 496 (MH ⁺)

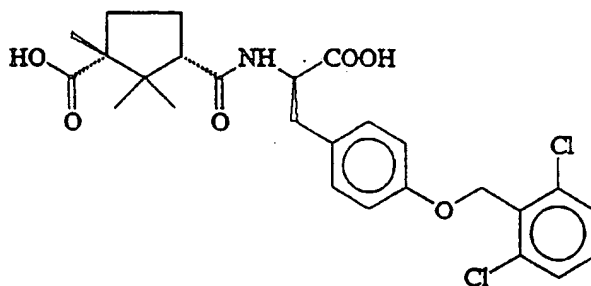
Table 2 (con't)

195

Ex. No.	R ⁰	Z ²	R ¹⁶	physicochemical property
37	CH ₃	CH ₂		gum . MS (m/z) : 492 (MH ⁺)
38	H	CH ₂		MS (m/z) : 478 (MH ⁺)

Example 39

(1*S*-*cis*)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-D-tyrosine
(C₂₆H₂₉Cl₂NO₆).

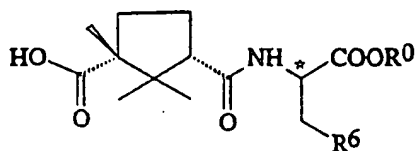


- 5 Example 39 is an isomer of Example 12 and is therefore synthesized in a manner similar to that of Example 12.

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Table 3

Examples 40 through 51:



(* : R- or S- form)

Ex. No.	*	R ⁰	R ⁶	physicochemical property
40	S	H		MS (m/z) : 452 (MH ⁺)
41	S	H		M.P. : 163-165°C MS (m/z) : 354 (MH ⁺)
42	S	H		MS (m/z) : 398 (MH ⁺)
43	S	H		MS (m/z) : 509 ([M-H] ⁻)

Table 3 (continued) 197

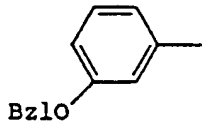
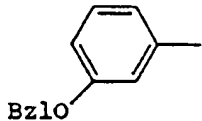
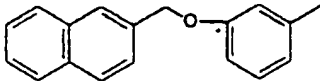
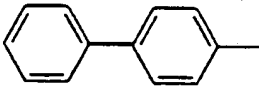
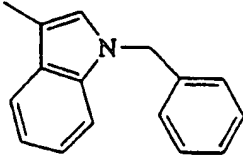
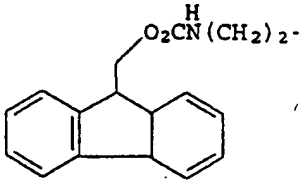
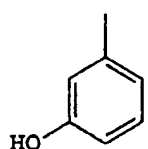
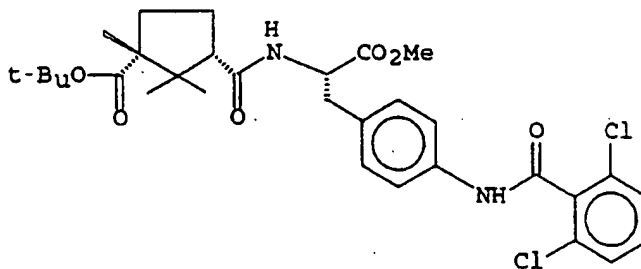
Ex. No.	*	R ⁰	R ⁶	physicochemical property
44	S	H	Ph	MS (m/z) : 348 (MH ⁺)
45	S	CH ₃		gum MS (m/z) : 468 (MH ⁺)
46	S	H		M.P. : 88-90°C MS (m/z) : 452 ([M-H] ⁻)
47	S	H		MS (m/z) : 502 ([M-H] ⁻)
48	S	H		MS (m/z) : 422 ([M-H] ⁻)
49	S	H		MS (m/z) : 475 ([M-H] ⁻)

Table 3 (continued) 198

Ex. No.	*	R ⁰	R ⁶	physicochemical property
50	S	H		MS (m/z) : 537 (MH ⁺)
51	R	H		MS (m/z) : 364 (MH ⁺)

Example 52. (1*S*-cis)-N-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester (C₂₇H₃₀Cl₂N₂O₆).

5



HCl gas was bubbled through a solution of N-(tert-butoxycarbonyl)-4-(2,6-dichlorobenzamido)-L-phenylalanine (800 mg) in MeOH (15 ml) for 5 minutes

and the mixture was stirred for 3 hr. at room temperature. Excess HCl was removed by bubbling N₂ through the mixture and the solvent was removed in vacuo. The residue was washed with ether and dried.

5 To the resulting solid was added THF (10 ml) containing DIEA (1.3 ml), BOP Reagent (938 mg) and (1S,3R)-3-(tert-butoxycarbonyl)-2,2,3-trimethylcyclopentanecarboxylic acid (480 mg), which was prepared by the saponification of methyl (1S,3R)-

10 3-(tert-butoxycarbonyl)-2,2,3-trimethylcyclopentanecarboxylate derived from methyl (1S,3R)-3-carboxy (or chlorocarbonyl)-2,2,3-trimethylcyclopentanecarboxylate and t-BuOH. The mixture was stirred overnight under N₂ and the solvent

15 was removed in vacuo.

1N HCl (10 ml) was added to the residue and the mixture was extracted with AcOEt. The extract was washed with 1N HCl, brine, sat. NaHCO₃, brine, sat. LiCl, and brine, dried over MgSO₄, and evaporated in

20 vacuo.

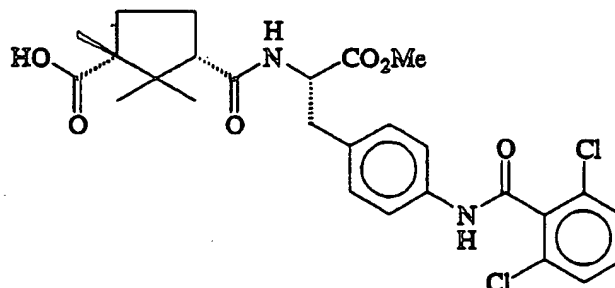
The residue was purified by column chromatography on silica gel (eluent; 3:2, Hexane/AcOEt) to give (1S-cis)-N-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-

25 dichlorobenzoyl)amino]-L-phenylalanine methyl ester (C₂₇H₃₀Cl₂N₂O₆) (1.05 g) as a colorless solid.

¹H NMR (300 MHz, CDCl₃), δ 7.58 (2H), 7.3-7.4 (3H), 7.11 (2H), 5.78 (1H), 4.8-5.0 (1H), 3.75 (3H), 3.10 (2H), 2.50 (1H), 2.0-2.2 (1H), 1.6-1.8 (1H), 1.44

30 (9H), 1.23 (3H), 1.16 (3H), 0.80 (3H); ¹³C NMR (75 MHz, CDCl₃), δ 175.07, 172.59, 172.17, 162.54, 136.32, 132.83, 132.48, 131.11, 130.01, 128.28, 120.56, 80.28, 56.76, 54.53, 53.12, 52.48, 46.46, 37.26, 32.41, 28.14, 23.06, 22.55, 22.06, 20.68; ESMS (m/z) 605 (MH⁺); Anal. Calcd for C₃₁H₃₈Cl₂N₂O₆ · 1/2 H₂O: C, 60.53; H, 6.35; N, 4.56; Found: C, 60.71; H, 6.31; N, 4.52. MS(m/z): 605 (MH⁺).

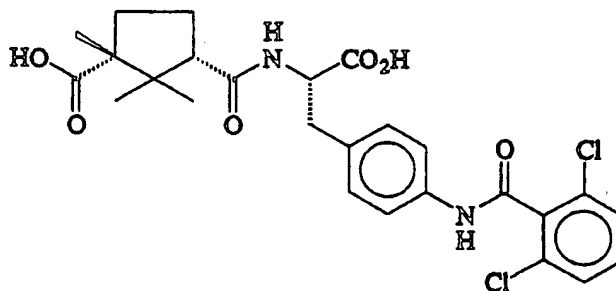
Example 53. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine methyl ester ($C_{27}H_{30}Cl_2N_2O_6$).



- 5 TFA (1.5 ml) was added to a solution of (1*S*-*cis*)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine methyl ester ($C_{27}H_{30}Cl_2N_2O_6$) (290 mg) in CH_2Cl_2 (1.5 ml) and the mixture
- 10 was stirred for 3 hr. The solvent was removed in vacuo and the residue was triturated with ether/ $CHCl_3$ to give (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine methyl ester (180 mg)
- 15 as a colorless powder.
- 1H NMR (300 MHz, Acetone- d_6), δ 9.75 (1H), 7.71 (2H), 7.4-7.6 (3H), 7.25 (2H), 7.12 (1H), 4.7-4.85 (1H), 3.68 (3H), 3.08 (2H), 2.85 (1H), 2.5-2.6 (1H), 1.6-1.8 (1H), 1.4-1.5 (1H), 1.26 (3H), 1.19 (3H), 0.80 (3H);
- 20 ^{13}C NMR (75 MHz, Acetone- d_6), δ 176.29, 172.20, 172.11, 162.00, 137.49, 133.12, 131.85, 131.12, 129.71, 128.16, 119.59, 55.98, 53.63, 52.89, 51.37, 46.14, 36.67, 32.47, 22.57, 22.04, 21.41, 20.74; ESMS (m/z) 549 (MH^+); Anal. Calcd for $C_{27}H_{30}Cl_2N_2O_6 \cdot 1/2 H_2O$: C, 58.02; H, 5.55; N, 5.01; Found: C, 58.70; H, 5.53; N, 5.01. MS (m/z): 549 (MH^+)
- 25

201

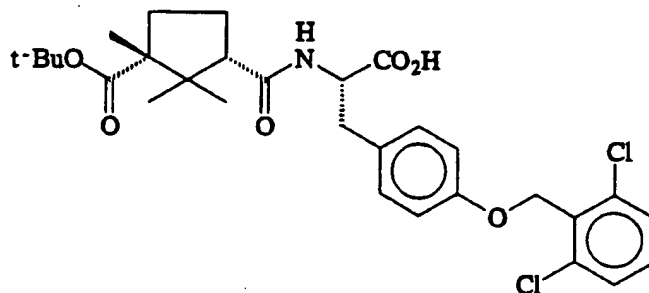
Example 54. (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$).



- 5 A solution of LiOH (19 mg) in H₂O (1 ml) was added to a solution of (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester ($C_{27}H_{30}Cl_2N_2O_6$) (108 mg) in THF (4 ml)/MeOH (1 ml). The
- 10 mixture was stirred for 2 hr, acidified with 1N HCl (15 ml), and extracted with AcOEt. The extract was washed with brine, dried over MgSO₄, and evaporated in vacuo to give (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (80 mg), m.p. 231-
- 15 233°C.
- ¹H NMR (300 MHz, Acetone-*d*₆). δ 9.72 (1H), 7.71 (2H), 7.47-7.48 (3H), 7.27 (2H), 7.07 (1H), 4.78-4.85 (1H), 3.15 (2H), 2.85 (1H), 2.5-2.6 (1H), 1.6-1.8 (1H), 1.4-1.5 (1H), 1.26 (3H), 1.19 (3H), 0.81 (3H); ¹³C NMR (75
- 20 MHz, Acetone-*d*₆). δ 177.67, 173.83, 173.62, 163.32, 138.74, 134.64, 133.17, 132.42, 131.10, 129.47, 120.88, 57.29, 54.69, 54.28, 47.47, 37.93, 33.81, 23.91, 23.39, 22.73, 22.08; ESMS (m/z) 535 (MH⁺), 533 (M-H)⁻; Anal. Calcd for $C_{26}H_{28}Cl_2N_2O_6 \cdot 1/2 H_2O$: C, 57.46; H, 5.34; N, 5.15; Found: C, 57.48; H, 5.38; N, 5.15. MS(m/z): 533 ([M-H]⁻); MS(m/z): 578 (MH⁺)
- 25

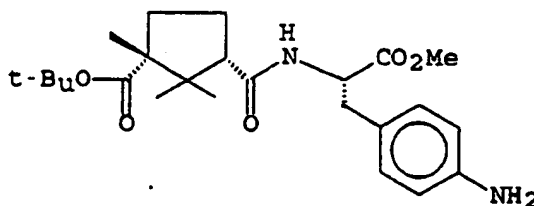
202

Example 55. (1*S*-*cis*)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine



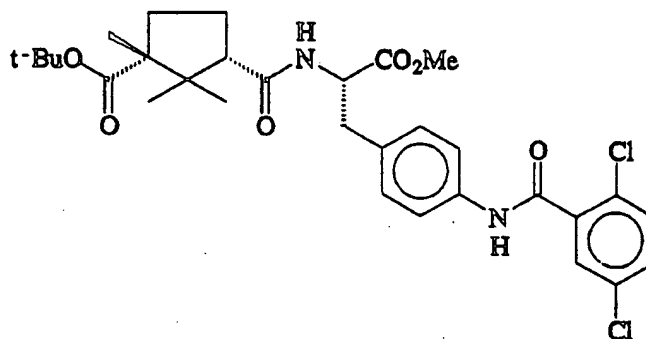
5 LiOH (177 mg) in H₂O (10 ml) was added to a mixture of (1*S*-*cis*)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine methyl ester (2.18
10 g) in THF (10 ml)/MeOH (5 ml) and the mixture was stirred at room temperature for 3 hr, acidified with 1N HCl (20 ml), and extracted with AcOEt. The extract was dried over Na₂SO₄ and the solvent was removed in vacuo to give (1*S*-*cis*)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-*O*-[(2,6-dichloro-
15 phenyl)methyl]-*L*-tyrosine (2.07 g). MS(*m/z*): 578 (MH⁺).

Example 56. (1*S*-*cis*)-4-Amino-*N*-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-*L*-phenylalanine methyl ester



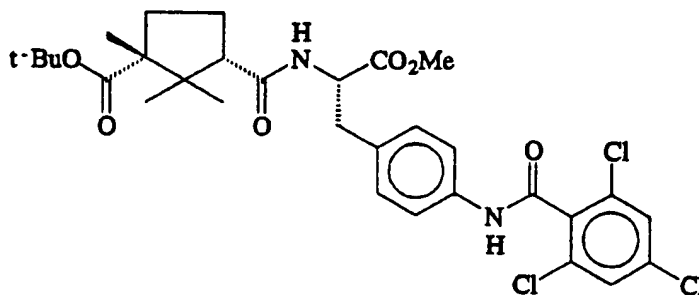
Two methods for the preparation of Example 56 are taught according to Scheme 5a and 5b.

Example 57. (1*S*-cis)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,5-dichlorobenzoyl)amino]-*L*-phenylalanine methyl ester.



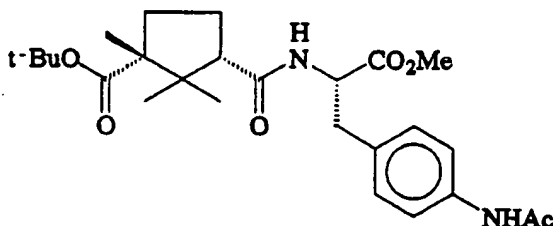
BOP-Cl (425 mg) and 2,5-dichlorobenzoic acid (319 mg) were added to a mixture of (1*S*-cis)-4-Amino-*N*-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-*L*-phenylalanine methyl ester (433 mg) and DIEA (0.7 ml) in CH₂Cl₂ (5 ml). The mixture was stirred for 3 hr. at room temperature, acidified with 1*N* HCl (50 ml) and extracted with CH₂Cl₂. The extract was dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent; Hexane → 50% Hexane/AcOEt) to give (1*S*-cis)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,5-dichlorobenzoyl)amino]-*L*-phenylalanine methyl ester (804 mg). MS (*m/z*): 605 (MH⁺).

Example 58. (1*S*-cis)-N-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,4,6-trichlorobenzoyl)amino]-L-phenylalanine methyl ester.



The preparation of Example 58 is taught by Scheme 13.

Example 59. (1*S*-cis)-4-Acetylamino-N-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-L-phenylalanine methyl ester.



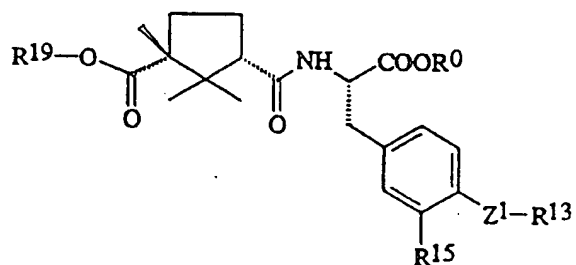
Acetic anhydride (1 ml) was added to a mixture of (1*S*-cis)-4-Amino-N-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-L-phenylalanine methyl ester (710 mg) and DIEA (4 ml) in CH₂Cl₂ (5 ml). The mixture was stirred for 30 minutes at room temperature and partitioned between sat. NaHCO₃ and AcOEt. The organic layer was dried over Na₂SO₄ and the solvent was removed in vacuo. The residue was

purified by column chromatography on silica gel
(eluent; Hexane \rightarrow EtOH /AcOEt(1:1)) to give (1*S*-cis)-
4-Acetylamino-N-[(3-[(1,1-dimethylethoxy)carbonyl]-
2,2,3-trimethylcyclopentyl)carbonyl]-L-phenylalanine
5 methyl ester (669 mg). MS(m/z):475(MH⁺).

Examples 60-153 were prepared in a similar
manner, as described in Examples 52-59, and are shown
in Table 4.

Table 4

Examples 60 through 153:



Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
60	H	CH ₃		single bond	OH	gum MS (m/z) : 565 (MH ⁺)
61	H	H		single bond	OH	M.P. : 168-171°C MS (m/z) : 549 ([M-H] ⁺)

Table 4 (Continued) 206

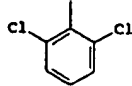
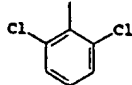
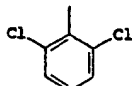
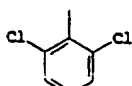
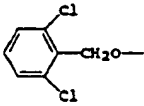
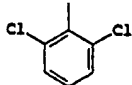
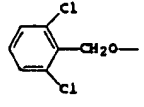
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
62	H	CH ₃	NO ₂	-OCH ₂ -		gum MS (m/z) : 581 (MH ⁺)
63	H	H	NO ₂	-OCH ₂ -		M.P. : 92-94°C MS (m/z) : 565 ([M-H] ⁻)
64	H	CH ₃	OH	-OCH ₂ -		gum MS (m/z) : 552 (MH ⁺)
65	H	H	OH	-OCH ₂ -		MS (m/z) : 538 (MH ⁺)
66	H	H		-OCH ₂ -		M.P. : 118-121°C MS (m/z) : 696 (MH ⁺)
67	H	H		single bond	OH	M.P. : 236-238°C MS (m/z) : 538 (MH ⁺)

Table 4 (Continued) 207

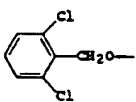
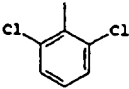
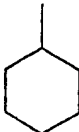
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
68	H	H	NO ₂	single bond	OH	M.P.: 122-125°C MS (m/z): 407 ([M-H] ⁺)
69	H	H	CH ₃ CO	single bond	OH	M.P.: 105-108°C MS (m/z): 404 ([M-H] ⁺)
70	H	CH ₃		-OCH ₂ -		gum MS (m/z): 710 (MH ⁺)
71	H	CH ₃	NO ₂	single bond	OH	gum MS (m/z): 423 (MH ⁺)
72	H	CH ₃	H	-NHCO-	PhCH ₂ O	gum MS (m/z): 511 (MH ⁺)
73	H	H	H	-NHCO-	PhCH ₂ O	M.P.: 95-97°C MS (m/z): 495 ([M-H] ⁺)
74	H	CH ₃	H	-NHCO-		gum MS (m/z): 487 (MH ⁺)

Table 4 (Continued) 208

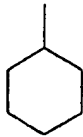
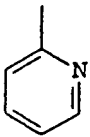
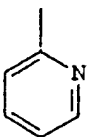
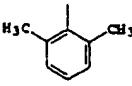
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
75	H	H	H	-NHCO-		M.P.: 151-154°C MS (m/z): 471 ([M-H] ⁻)
76	H	CH ₃	H	-NHCO-		gum MS (m/z): 482 (MH ⁺)
77	H	H	H	-NHCO-		M.P.: 102-104°C MS (m/z): 466 ([M-H] ⁻)
78	H	CH ₃	H	-NHCO-	CH ₃	gum MS (m/z): 419 (MH ⁺)
79	H	H	H	-NHCO-	CH ₃	M.P.: 238-240°C MS (m/z): 403 ([M-H] ⁻)
80	H	CH ₃	H	-NHCO-		gum MS (m/z): 509 (MH ⁺)

Table 4 (Continued) 209

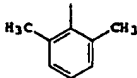
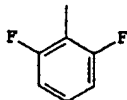
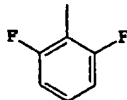
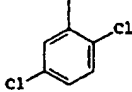
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
81	H	H	H	-NHCO-		M.P.: 195-198°C MS (m/z) : 495 (MH ⁺) ; MS (m/z) : 493 ([M-H] ⁺)
82	H	CH ₃	H	-NHCO-		gum MS (m/z) : 517 (MH ⁺)
83	H	H	H	-NHCO-		M.P.: 150-152°C MS (m/z) : 503 (MH ⁺)
84	H	CH ₃	H	-NHCO-	Ph	gum MS (m/z) : 481 (MH ⁺)
85	H	H	H	-NHCO-	Ph	M.P.: 145-148°C MS (m/z) : 465 ([M-H] ⁺)
86	H	CH ₃	H	-NHCO-		gum MS (m/z) : 549 (MH ⁺)

Table 4 (Continued) 210

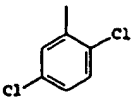
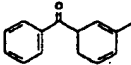
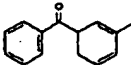
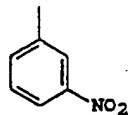
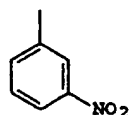
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
87	H	H	H	-NHCO-		M.P.: 155-158°C MS (m/z): 533 ([M-H] ⁺)
88	H	CH ₃	H	-NHCO-		gum MS (m/z): 585 (MH ⁺)
89	H	H	H	-NHCO-		M.P.: 190-193°C MS (m/z): 569 ([M-H] ⁺)
90	H	CH ₃	H	-NHCO-		gum MS (m/z): 526 (MH ⁺)
91	H	H	H	-NHCO-		M.P.: 146-149°C MS (m/z): 512 (MH ⁺)

Table 4 (Continued) 211

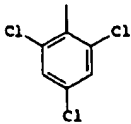
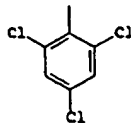
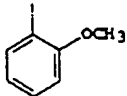
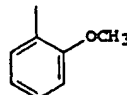
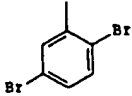
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
92	H	CH ₃	H	-NHCO-		gum MS (m/z) : 583 (MH ⁺)
93	H	H	H	-NHCO-		MS (m/z) : 569 ([M-H] ⁺)
94	H	CH ₃	H	-NHCO-		gum MS (m/z) : 511 (MH ⁺)
95	H	H	H	-NHCO-		M.P. : 140-143°C MS (m/z) : 497 (MH ⁺)
96	H	CH ₃	H	-NHCO-		gum MS (m/z) : 637 (MH ⁺)

Table 4 (Continued) 212

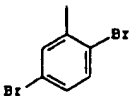
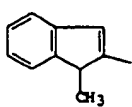
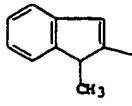
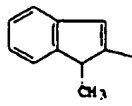
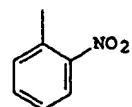
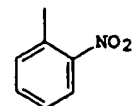
Ex. No.	R ¹⁹	R ²⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
97	H	H	H	-NHCO-		M.P.: 170-173°C MS (m/z): 623 ([M-H] ⁺)
98	t-Bu	CH ₃	H	-NHCO-		gum MS (m/z): 589 (MH ⁺)
99	H	CH ₃	H	-NHCO-		gum MS (m/z): 533 (MH ⁺)
100	H	H	H	-NHCO-		M.P.: 165°C (dec.) MS (m/z): 517 ([M-H] ⁺)
101	H	CH ₃	H	-NHCO-		gum MS (m/z): 526 (MH ⁺)
102	H	H	H	-NHCO-		MS (m/z): 512 (MH ⁺)

Table 4 (Continued) 213

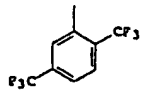
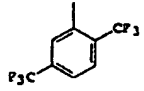
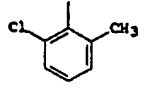
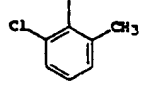
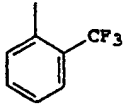
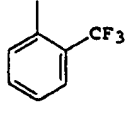
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
103	H	CH ₃	H	-NHCO-		gum MS (m/z) : 617 (MH ⁺)
104	H	H	H	-NHCO-		M.P.: 148-150°C MS (m/z) : 601 ([M-H] ⁻)
105	H	CH ₃	H	-NHCO-		gum MS (m/z) : 529 (MH ⁺)
106	H	H	H	-NHCO-		M.P.: 165-168°C MS (m/z) : 513 ([M-H] ⁻)
107	H	CH ₃	H	-NHCO-		gum MS (m/z) : 549 (MH ⁺)
108	H	H	H	-NHCO-		M.P.: 180-183°C MS (m/z) : 533 ([M-H] ⁻)

Table 4 (Continued) 214

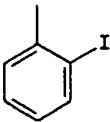
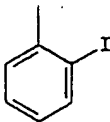
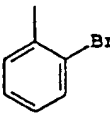
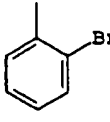
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
109	H	CH ₃	H	-NHCO-		gum MS (m/z) : 607 (MH ⁺)
110	H	H	H	-NHCO-		M.P. : 162-165°C MS (m/z) : 591 ([M-H] ⁺)
111	H	CH ₃	H	-NHCO-		gum MS (m/z) : 559, 561 (M ⁺)
112	H	H	H	-NHCO-		M.P. : 156-158°C MS (m/z) : 543 ([M-H] ⁺)

Table 4 (Continued) 215

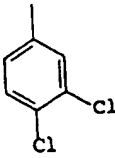
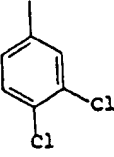
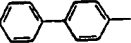
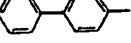
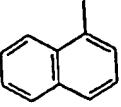
Ex. No.	R ¹⁹	R ²⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
113	H	CH ₃	H	-NHCO-		gum MS (m/z) : 549 (MH ⁺)
114	H	H	H	-NHCO-		M.P. : 155-157°C MS (m/z) : 533 ([M-H] ⁻)
115	H	CH ₃	H	-NHCO-		gum MS (m/z) : 557 (MH ⁺)
116	H	H	H	-NHCO-		M.P. : 162-165°C MS (m/z) : 541 ([M-H] ⁻)
117	H	CH ₃	H	-NHCO-		gum MS (m/z) : 531 (MH ⁺)

Table 4 (Continued) 216

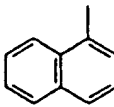
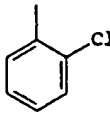
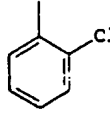
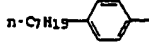
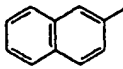
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
118	H	H	H	-NHCO-		M.P.: 235-237°C MS (m/z): 517 ([M-H] ⁺)
119	H	CH ₃	H	-NHCO-		gum MS (m/z): 515 (MH ⁺)
120	H	H	H	-NHCO-		M.P.: 143-145°C MS (m/z): 499 ([M-H] ⁺)
121	H	H	H	-NHCO-	PhCH ₂ -	M.P.: 240-242°C MS (m/z): 479 ([M-H] ⁺)
122	H	H	H	-NHCO-		M.P.: 212-214°C MS (m/z): 563 ([M-H] ⁺)
123	H	CH ₃	H	-NHCO-		gum MS (m/z): 531 (MH ⁺)

Table 4 (Continued) 217

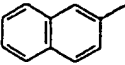
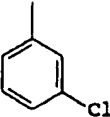
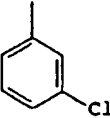

Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
124	H	H	H	-NHCO-		M.P.: 141-143°C MS (m/z): 515 ([M-H] ⁺)
125	H	CH ₃	H	-NHCO-		gum MS (m/z): 515 (MH ⁺)
126	H	H	H	-NHCO-		M.P.: 145-147°C MS (m/z): 499 ([M-H] ⁺)
127	H	CH ₃	H	-NHCO-		gum MS (m/z): 515 (MH ⁺)

Table 4 (Continued) 218

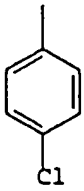
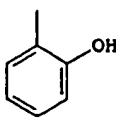
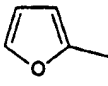
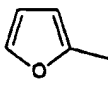
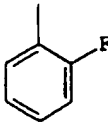
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
128	H	H	H	-NHCO-		M.P.: 185-188°C MS (m/z): 499 ([M-H] ⁻)
129	t-Bu	CH ₃	H	-NHCO-		gum MS (m/z): 553 (MH ⁺)
130	H	H	H	-NHCO-		M.P.: 158-161°C MS (m/z): 455 ([M-H] ⁻)
131	t-Bu	CH ₃	H	-NHCO-		gum MS (m/z): 527 (MH ⁺)
132	H	H	H	-NHCO-		M.P.: 117-120°C MS (m/z): 483 ([M-H] ⁻)

Table 4 (Continued) 219

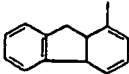
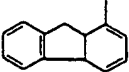
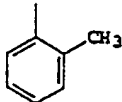
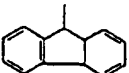
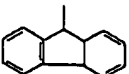
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
133	H	CH ₃	H	-NHCO-	i-Bu	gum MS (m/z) : 461 (MH ⁺)
134	H	H	H	-NHCO-	i-Bu	M.P.: 146-148°C MS (m/z) : 445 ([M-H] ⁺)
135	H	CH ₃	H	-NHCO-		gum MS (m/z) : 569 (MH ⁺)
136	H	H	H	-NHCO-		M.P.: 160-163°C MS (m/z) : 553 ([M-H] ⁺)
137	H	CH ₃	H	-NHCO-		gum MS (m/z) : 495 (MH ⁺)
138	H	CH ₃	H	-NHCO-		gum MS (m/z) : 569 (MH ⁺)
139	H	H	H	-NHCO-		M.P.: 166-169°C

Table 4 (Continued) 220

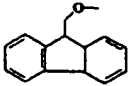
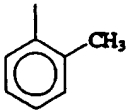
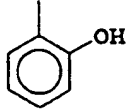
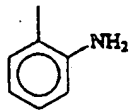
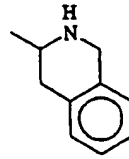
Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
140	H	CH ₃	H	-NHCO-		gum MS (m/z) : 599 (MH ⁺)
141	H	H	H	-NHCO-	i-BuO	M.P.: 125-128°C MS (m/z) : 461 ([M-H] ⁻)
142	H	H	H	-NHCO-		M.P.: 152-155°C MS (m/z) : 479 ([M-H] ⁻)
143	H	H	H	-NHCO-		M.P.: 148-150°C MS (m/z) : 481 ([M-H] ⁻)
144	H	H	H	-NHCO-		M.P.: 195-198°C MS (m/z) : 480 ([M-H] ⁻)
145	H	CH ₃	H	-NHCO-		gum MS (m/z) : 536 (MH ⁺)

Table 4 (Continued) 221

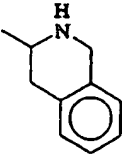
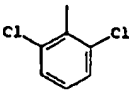
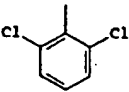
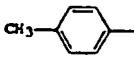
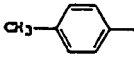
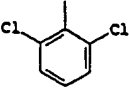
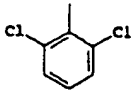
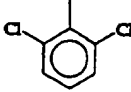
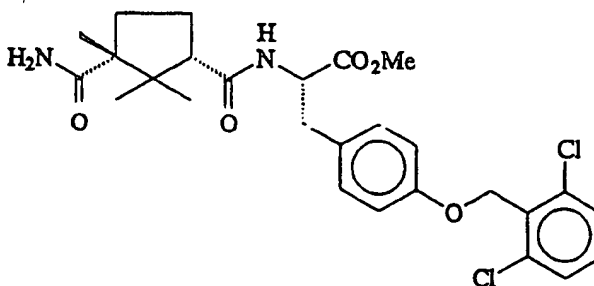
Ex. No.	R ¹⁹	R ²⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
146	H	H	H	-NHCO		M.P.: 208-211°C MS (m/z): 520 ([M-H] ⁺)
147	H	CH ₃	H	-NHSO ₂ -		gum MS (m/z): 585 (MH ⁺)
148	H	H	H	-NHSO ₂ -		M.P.: 224-226°C MS (m/z): 569 ([M-H] ⁺)
149	H	CH ₃	H	-NHSO ₂ -		gum MS (m/z): 531 (MH ⁺)
150	H	H	H	-NHSO ₂ -		M.P.: 220-223°C MS (m/z): 515 ([M-H] ⁺)
151	H	CH ₃	H	-NHCH ₂ -		gum MS (m/z): 535 (MH ⁺)

Table 4 (Continued) 222

Ex. No.	R ¹⁹	R ⁰	R ¹⁵	Z ¹	R ¹³	physico-chemical property
152	H	H	H	-NHCH ₂ -		M.P.: 100-103°C MS (m/z): 519 ([M-H] ⁺)
153	H	H	H	-CONH-		MS (m/z): 533 ([M-H] ⁺)

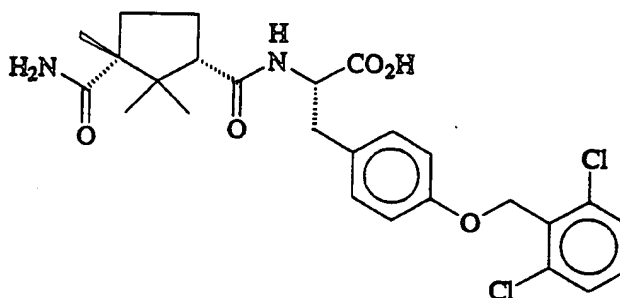
Example 154. (1*S*-cis)-N-[[3-(Aminocarbonyl)-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester.



- 5 BOP Reagent (674 mg) was added to a mixture of (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester (743 mg) and aq. NH₄OH (0.5 ml) in THF (10 ml). The mixture
- 10 was stirred for 24 hr. and sat. LiCl (15 ml) was added. The resulting mixture was extracted with AcOEt and the extract was dried over Na₂SO₄. The solvent was

removed in vacuo and the residue was purified by column chromatography on silica gel (eluent; Hexane → 90% AcOEt/Hexane) to give (1*S*-*cis*)-*N*-[[3-(Aminocarbonyl)-2,2,3-trimethylcyclopentyl]carbonyl]-
5 O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester (533 mg). MS(*m/z*): 535 (*MH*⁺).

Example 155. (1*S*-*cis*)-*N*-[[3-(Aminocarbonyl)-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine

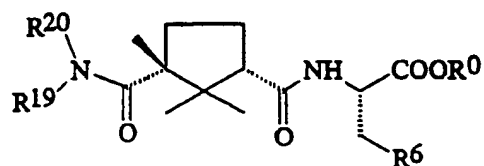


10 A solution of LiOH (119 mg) in H₂O (5 ml) was added to a mixture of (1*S*-*cis*)-*N*-[[3-(Aminocarbonyl)-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester (533
15 mg) in THF (5 ml)/MeOH (3 ml). The mixture was stirred for 3 hr. at room temperature, acidified with 1*N* HCl (20 ml), and extracted with AcOEt. The extract was dried over Na₂SO₄ and evaporated in vacuo to give
20 (1*S*-*cis*)-*N*-[[3-(Aminocarbonyl)-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine (466 mg), mp 102-104°C, MS (*m/z*): 519 (*[M-H]*⁻).

Examples 156-166 were prepared in a similar manner, as described in Examples 154 and 155 and are shown in Table 5.

Table 5

Examples 156 through 166:



Ex. No.	R ¹⁹	R ²⁰	R ⁰	R ⁶	physicochemical property
156		H	H		M.P.: 85-87°C MS (m/z): 533 ([M-H] ⁻)
157	Et	H	CH ₃		gum MS (m/z): 563 (MH ⁺)
158	Et	H	H		MS (m/z): 550 (MH ⁺)

Table 5 (continued) 225

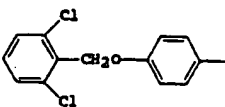
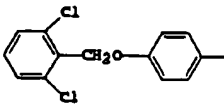
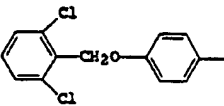
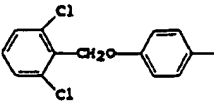
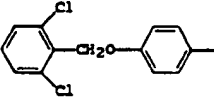
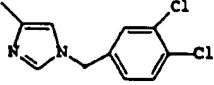
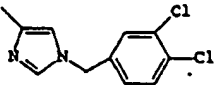
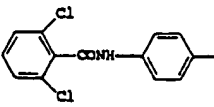
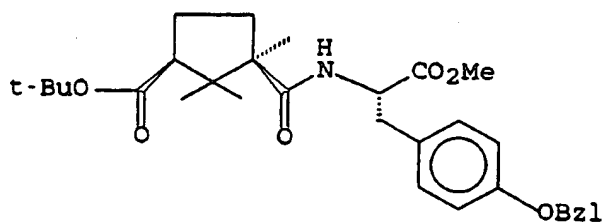
Ex. No.	R ¹⁹	R ²⁰	R ⁰	R ⁶	physicochemical property
159	Me	H	CH ₃		gum; ¹ H NMR (300MHz, CD ₃ OD), δ 7.3-7.4 (3H), 7.14 (2H), 6.95 (2H), 5.22 (2H), 4.71 (1H), 3.69 (3H), 3.12 (1H), 3.00 (1H), 2.39 (3H), 2.3-2.4 (1H), 2.0-2.1 (1H), 1.7-1.8 (1H), 1.4-1.5 (1H), 1.27 (3H), 1.18 (3H), 0.73 (3H).
160	Me	H	H		M.P.: 80-83°C MS(m/z): 533 ([M-H] ⁻)
161	Me	Me	H		¹ H NMR (300MHz, CDCl ₃), δ 7.3-7.4 (3H), 7.16 (2H), 7.00 (2H), 5.25 (2H), 4.75 (1H), 3.66 (3H), 3.22 (1H), 3.13 (1H), 2.5-2.7 (1H), 2.1-2.2 (1H), 2.05 (3H), 2.03 (3H), 1.7-1.8 (1H), 1.4-1.6 (1H), 1.20 (3H), 1.19 (3H), 0.73 (2H).

Table 5 (continued) 226

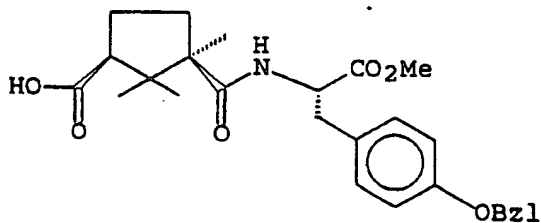
Ex. No.	R ¹⁹	R ²⁰	R ⁰	R ⁶	physicochemical property
162	MeO	H	CH ₃		gum MS (m/z) : 565 (MH ⁺)
163	MeO	H	H		M.P. : 70-72°C MS (m/z) : 551 ([M-H] ⁻)
164	Me	H	H		MS (m/z) : 509 (MH ⁺)
165	Et	H	H		MS (m/z) : 523 (MH ⁺)
166	H	H	H		M.P. : 196-198°C MS (m/z) : 532 ([M-H] ⁻)

Example 167. (1*R*-*cis*)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-1,2,2-trimethylcyclopentyl]carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine methyl ester



5 Example 167 was prepared from *O*-benzyl-*L*-tyrosine methyl ester hydrochloride and (1*R*,3*S*)-3-(tert-butoxycarbonyl)-1,2,2-trimethylcyclopentanecarboxylic acid in a similar manner as described in Example 52. Physicochemical property: gum, MS (*m/z*):524 (*MH*⁺).

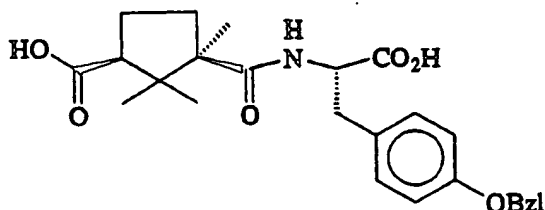
10 Example 168. (1*R*-*cis*)-*N*-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine methyl ester (C₂₇H₃₃NO₆).



15 Example 168 was prepared in a similar manner as described in Example 53. Physicochemical property: gum; MS (*m/z*):468 (*MH*⁺); MP 191-192°C (d).

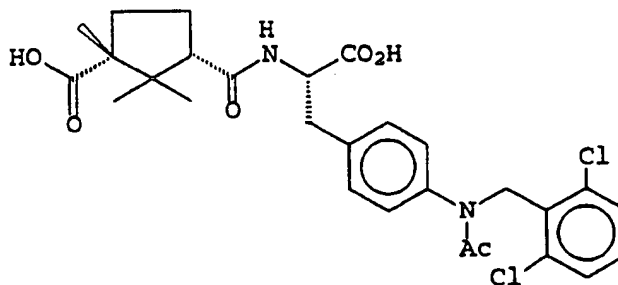
228

Example 169. (1*R*-*cis*)-*N*-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine (C₂₆H₃₁NO₆).



Example 169 was prepared in a similar manner as described in Example 54, MS (m/z):454 (MH⁺).

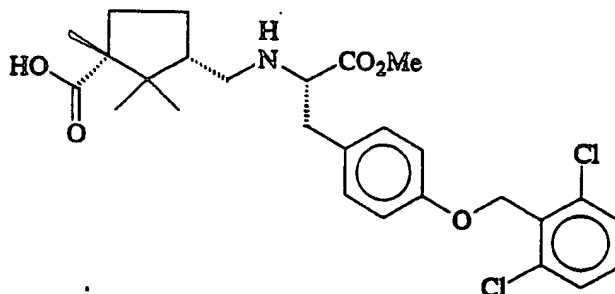
Example 170. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[*N*-acetyl-*N*-[(2,6-dichlorophenyl)methyl]amino]-*L*-phenylalanine methyl ester



(1*S*-*cis*)-*N*-[(3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl)carbonyl]-4-[*N*-[(2,6-dichlorophenyl)methyl]amino]-*L*-phenylalanine methyl ester (0.29 g), which was derived from 4-[[*N*-(2,6-dichlorophenyl)methyl]amino]-*L*-phenylalanine methyl ester in a similar manner as described in Example 52, was dissolved in pyridine (3 ml) and Ac₂O (2.5 ml) was added. The mixture was stirred overnight, evaporated in vacuo, and extracted with AcOEt. The extract was washed with aq. HCl, brine, sat. NaHCO₃, brine, and

dried over Na_2SO_4 . The solvent was removed in vacuo to give (1*S*-cis)-*N*-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[[*N*-acetyl-*N*-[(2,6-dichlorophenyl)methyl]amino]-*L*-phenylalanine methyl ester (0.24 g). The obtained diester was treated in a similar manner as described in Examples 53 and 54 to give (1*S*-cis)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[*N*-acetyl-*N*-[(2,6-dichlorophenyl)methyl]amino]-*L*-phenylalanine methyl ester as a colorless solid, mp 241-244°C, MS (*m/z*): 561 ($[\text{M}-\text{H}]^-$).

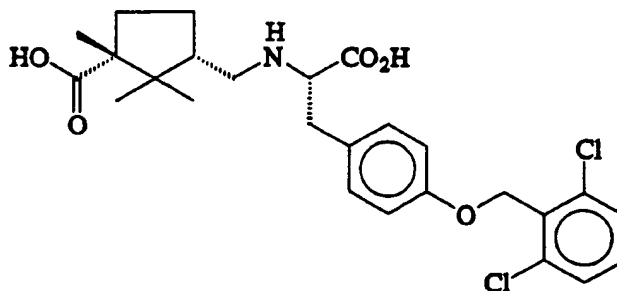
Example 171. (1*S*-cis)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)methyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine methyl ester ($\text{C}_{27}\text{H}_{33}\text{Cl}_2\text{NO}_5$).



NaCNBH_3 (104 mg) was added to a mixture of *O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine methyl ester (490 mg), (1*R*,*cis*)-3-formyl-1,2,2-trimethylcyclopentanecarboxylic acid, (1*R*,5*S*)-4-hydroxy-1,8,8-trimethyl-3-oxabicyclo[3,2,1]-octane-2-one (153 mg), AcOH (0.5 ml), and MeOH (25 ml) under argon. The mixture was stirred for 72 hr. at room temperature. The solvent was removed in vacuo and 10% HCl (20 ml) was added. The resulting mixture was stirred for 2 hr. and extracted with AcOEt. The extract was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on

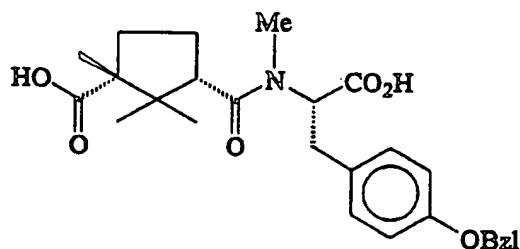
silica gel (eluent; 10% AcOEt/Hexane) to give (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)methyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine methyl ester (75 mg), MS(*m/z*): 522(MH⁺).

- 5 Example 172. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)methyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine (C₂₆H₃₁Cl₂NO₃).



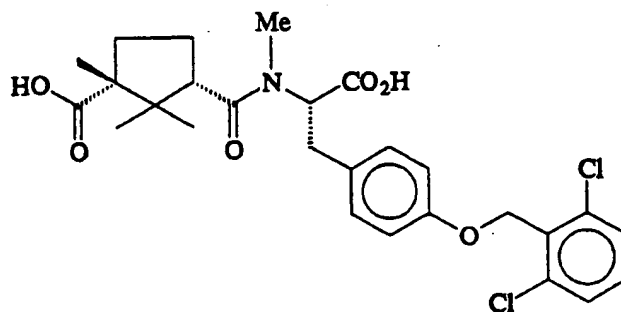
- 10 A solution of LiOH (33 mg) in H₂O (2 ml) was added to a mixture of (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)methyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine methyl ester (C₂₇H₃₃Cl₂NO₃) (71 mg) in THF (2 ml). The mixture was stirred for 5 hr. at room temperature, neutralized with 1*N* HCl, and extracted with AcOEt. The extract was dried over Na₂SO₄ and evaporated in vacuo to give (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)methyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine (40 mg), mp 135-138°C, MS(*m/z*): 508(MH⁺).
- 20

Example 173. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*N*-methyl-*O*-(phenylmethyl)-*L*-tyrosine ($C_{27}H_{33}NO_6$).



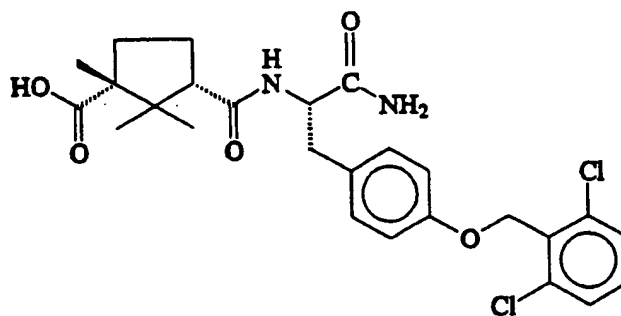
- 5 (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-(phenylmethyl)-*L*-tyrosine ($C_{26}H_{31}NO_6$) (52 mg) was added to a suspension of NaH (20.5 mg, 60% in oil) in DMF (5 ml) and the mixture was stirred for 10 min at room temperature.
- 10 After addition of MeI (43 ml), the mixture was stirred for 14 hr. and quenched with H₂O. The resulting mixture was extracted with ether. The extract was evaporated in vacuo and the residue was subjected to saponification using aq. LiOH in THF in a similar
- 15 manner as described in Example 54. The saponification was carried out for 2 hr. and the mixture was acidified with 1N HCl (10 ml) and extracted with AcOEt. The extract was dried over Na₂SO₄, evaporated in vacuo, and the residue was purified by column
- 20 chromatography on silica gel (eluent; 10% MeOH/CH₂Cl₂) to give (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*N*-methyl-*O*-(phenylmethyl)-*L*-tyrosine (40 mg), MS(*m/z*): 466 ([*M*-H]⁻).

Example 174. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-[(2,6-dichlorophenyl)methyl]-*N*-methyl-*L*-tyrosine ($C_{27}H_{31}Cl_2NO_6$).



5 Example 174 was prepared from *N*-(tert-butoxycarbonyl)-*O*-[(2,6-dichlorophenyl)methyl]-*N*-methyl-*L*-tyrosine and (1*S*,3*R*)-3-(tert-butoxycarbonyl)-2,2,3-trimethylcyclopentanecarboxylic acid in a similar manner as described in Example 52, 53 and 54,
10 mp 108-110°C, MS (*m/z*):536 (*MH*⁺).

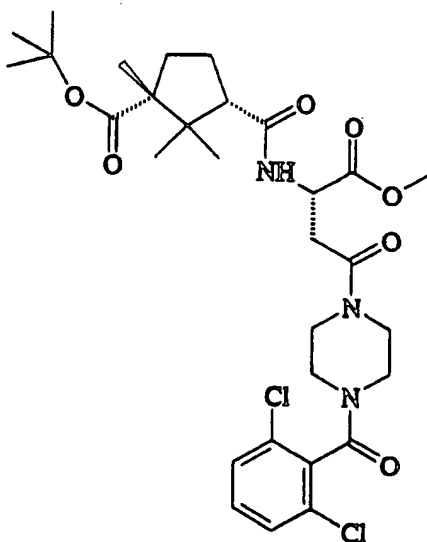
Example 175. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosinamide ($C_{26}H_{30}Cl_2N_2O_5$).



15 NaCN (10 mg) was added to a solution of (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-

[2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester (306 mg) in MeOH (10 ml) in a thick walled tube. 15-20 ml of NH_3 was condensed into the mixture at -78°C . The tube was sealed and warmed to room temperature. After 48 hr. stirring, the mixture was cooled to -78°C and the sealed tube was opened. The mixture was warmed to room temperature and excess NH_3 was removed by bubbling N_2 . The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (eluent; AcOEt \rightarrow 10% MeOH/AcOEt) to give (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosinamide (258 mg), mp $120-122^\circ\text{C}$, MS (m/z): 519 ([M-H] $^-$).

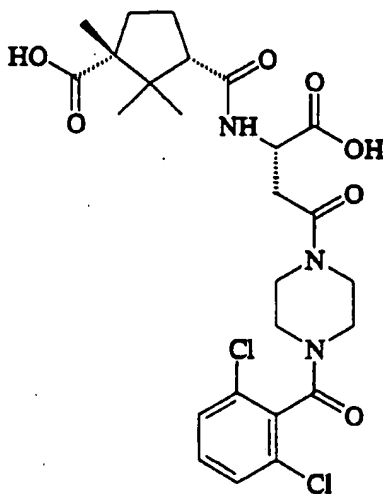
Example 176 [1S-[1 α (R*),3 α]]-4-(2,6-Dichlorobenzoyl)- α -[[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]amino]- γ -oxo-1-piperazinebutanoic acid methyl ester



The synthesis of Example 176 is taught by Scheme 17.

Example 177

[1S-[1 α (R*),3 α]]- α -[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-4-(2,6-dichlorobenzoyl)- γ -oxo-1-piperazinebutanoic acid

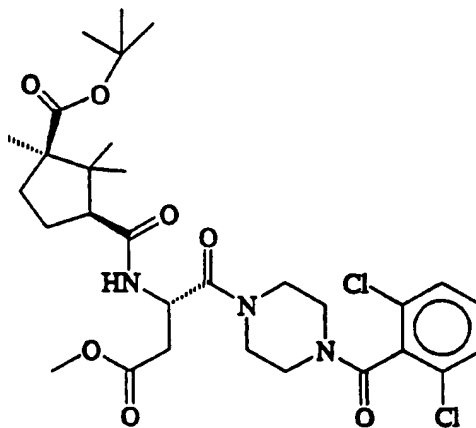


5 The synthesis of Example 177 is taught by Scheme 17.

Example 178

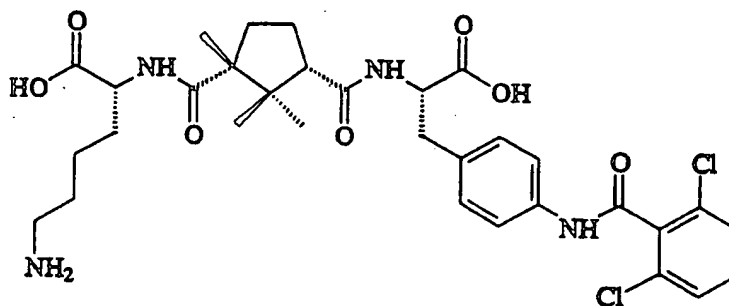
[1S-[1 α (R*),3 α]]-4-(2,6-Dichlorobenzoyl)- β -[[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl)carbonyl]amino]- γ -oxo-1-piperazinebutanoic acid methyl ester

10



The synthesis of Example 178 is taught by Scheme 18.

Example 179. [1S-[1 α ,3 α (R*)]-N-[[3-[[[5-Amino-1-carboxypentyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzyl)amino]-L-phenylalanine



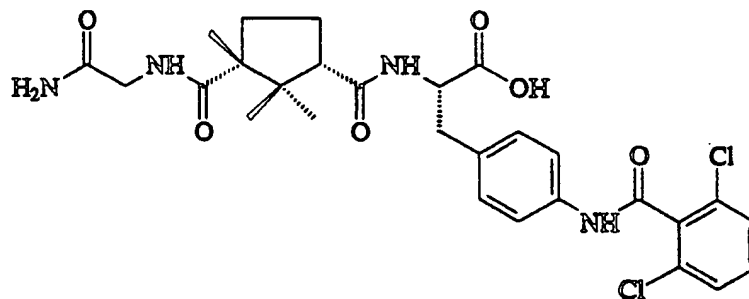
(1) To a solution of N-(tert-butoxycarbonyl)-4-(2,6-dichlorobenzamido)-L-phenylalanine (9.25 g) in DMF (80-100 ml) was added Merrifield resin (10.0 g, 10.0 meq/g, Novabiochem) and anhydrous potassium fluoride (1.57 g). The reaction mixture was stirred for 1 day at 80°C and the resulting resin bound amino acid derivative was collected by filtration, washed thoroughly with DMF, 50% aqueous DMF, CH₃OH, CH₂Cl₂, CH₃OH, and then dried in vacuo to give the resin bound N-(tert-butoxycarbonyl)-4-(2,6-dichlorobenzamido)-L-phenylalanine (0.53 meq/g). Substitution of the amino acid derivative onto the resin was estimated using the picric acid method.

(2) To the obtained resin (1.0 g, 0.53 meq/g) was added 50% TFA/CH₂Cl₂ (10-15ml) and the mixture was stirred for 30 min. The resin was collected by filtration, washed with CH₂Cl₂, CH₃OH, and CH₂Cl₂. To the resin bound 4-(2,6-dichlorobenzamido)-L-phenylalanine was added a mixture of (1S, 3R)-3-(tert-butoxycarbonyl)-2,2,3-trimethylcyclopentanecarboxylic

- acid (408 mg), 0.5M HBTU-HOBT (3.3 ml) in DMF, DIEA (0.694 ml), DMF (10-15 ml) and the mixture was vortexed for 2 hrs. at room temperature. The resin was collected by filtration, washed with DMF, CH₂Cl₂, CH₃OH, CH₂Cl₂ to give a resin bound (1S-cis)-N-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (0.990 g). To the mixture
- 10 (3) To the resin (0.390 g, 0.21 meq/g) was added 50% TFA/CH₂Cl₂ (4-5 ml) and the mixture was stirred for 2 hrs. The resin was collected by filtration, washed with CH₂Cl₂, CH₃OH, and CH₂Cl₂. To the resin bound (1S-cis)-N-[[3-Carboxy-2,2,3-
- 15 trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine was added a mixture of N⁶-(tert-butoxycarbonyl)-L-lysine tert-butyl ester (0.210 g), 0.5M HBTU-HOBT (1.5 ml) in DMF, DIEA (0.270 ml) and the mixture was vortexed for 2
- 20 hrs. The resin was collected by filtration, washed with DMF, CH₂Cl₂, CH₃OH, and CH₂Cl₂. To the obtained resin was added 50% TFA/CH₂Cl₂ (4-5 ml) and the mixture was stirred for 30 min. The resin was collected by filtration, washed with CH₂Cl₂, CH₃OH, and
- 25 CH₂Cl₂. To the resin was added THF (3 ml), CH₃OH (0.9 ml) and 2N LiOH (0.3 ml). The mixture was stirred for 15 mins and filtered to a test tube (13 x 100 mm). The resin was washed with THF/5% CH₃OH and the combined filtrate was evaporated. The residue was
- 30 diluted with H₂O (1ml) and acidified with 1N HCl. The precipitate was centrifuged. The supernatant was decanted, and the pellet was washed with H₂O. The residue was lyophilized to give a colorless solid (100 mg).
- 35 (4) The solid (80 mg) was purified by a Water Delta Prep 3000 system (Waters, Milford, Massachusetts)

equipped with a reversed phase silica C18 column (4.7 cm x 30.0 cm), using a linear gradient of increasing acetonitrile in an aqueous solution of triethylammonium phosphate (TEAP) (prepared by diluting phosphoric acid (25 ml) and triethylamine (50 ml) to 6000 ml of deionized water, pH -5.5). The fractions containing desired compound was desalted with 0.1% acetic acid using the above system. The collected fractions were lyophilized to give [1S-
 10 [1 α ,3 α (R*)]-N-[[3-[[[(5-Amino-1-carboxypentyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (Example 179) as a colorless solid (10 mg), ESMS:661 (M-H)).

15 Example 180. (1S-cis)-N-[[3-[[[(2-Amino-2-oxoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (C₂₈H₃₂Cl₂N₄O₆).

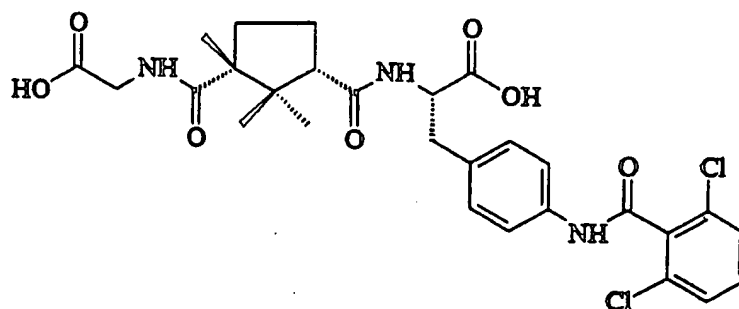


20 The synthesis of Example 180 is taught by Scheme 8, 8-G: wherein R⁰⁻¹ = H, R²⁻³ = H, R⁴ = H, R⁵ = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl, Stereochemistry = (1S-cis) - L. Accordingly, the synthesis of
 25 (1S-cis)-N-[[3-[[[(2-Amino-2-oxoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichloro-

benzoyl)amino]-L-phenylalanine ($C_{28}H_{32}Cl_2N_4O_6$) is as follows.

To 8-F-1 (8-F: $R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 =$
4-[(2,6-dichlorobenzoyl)amino]-phenyl, Stereochemistry
5 = (1S-cis)-L) (1.05g, 1.7mmol), dissolved in methanol
(30mL), is added a solution of $LiOH \cdot 2H_2O$ (0.32g,
7.65mmol) in water (10mL), dropwise over 15 minutes.
The mixture stirs for 18 hours at room temperature and
the pH is then adjusted to ca. 7 by the careful
10 addition of 1N aq. HCl. The majority of the methanol,
is removed in vacuo and the pH of the resulting
solution is adjusted to ca. 2 with 1N aq. HCl. The
resulting flocculent white precipitate is isolated by
filtration and dried. The solid is crushed and washed
15 with water (2X10mL) and dried in vacuo at 50°C to give
0.97g (97%) of Example 180 (8-G: $R^{8-1} = H$, $R^{8-2} = H$, $R^4 =$
 H , $R^6 = 4-[(2,6-$
dichlorobenzoyl)amino]-phenyl) as a white, powdery
solid.
20 MP: 203-205°C; 1H NMR (300MHz, DMSO- d_6): δ 12.51(brs,
1H), 10.70(s, 1H), 7.75(m, 1H), 7.45-7.57(3H), 7.33(m,
1H), 7.20(m, 2H), 7.11(brs, 1H), 6.92(brs, 1H),
4.43(m, 1H), 3.63(m, 1H), 3.47m, 2H), 3.30(s, 2H),
3.01(m, 1H), 2.84(m, 1H), 2.31(m, 1H), 1.87(m, 1H),
25 1.55(m, 1H), 1.31(m, 1H), 1.17(s, 3H), 1.08(s, 3H),
0.59(s, 3H); IR (Mull): 3511, 3325, 3128, 3082, 2868,
1722, 1697, 1664, 1614, 1555, 1537, 1417, 1337, 1246,
799; MS (FAB) m/z (rel. intensity) 591(M+H, base),
517(32), 335(26), 239(32), 173(39), 109(63), 57(80);
30 HRMS (FAB) calcd for $C_{28}H_{32}Cl_2N_4O_6 + H^+$ 591.1777, found
591.1747.

Example 181. (1S-cis)-N-[[3-
[[[(Carboxymethyl)amino]carbonyl]-2,2,3-
trimethylcyclopentyl]carbonyl]-4-[(2,6-
35 dichlorobenzoyl)amino]-L-phenylalanine
($C_{28}H_{31}Cl_2N_3O_7$).



The synthesis of Example 181 is taught by scheme 7, 7-G: wherein $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2H$, $R^6 = 4-[(2,6-$
Dichlorobenzoyl)amino]phenyl and

Stereochemistry = (1S-cis) - L. Accordingly, (1S-

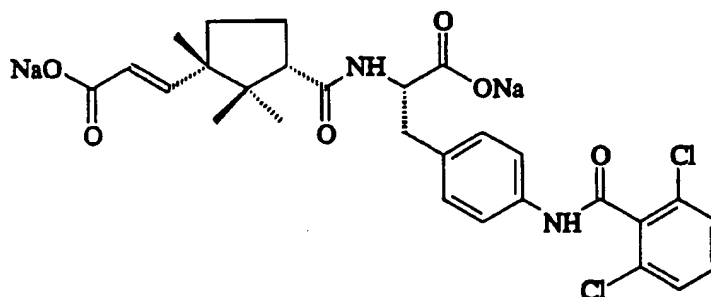
5 cis)-N-[[3-[[[(Carboxymethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{28}H_{31}Cl_2N_3O_7$) is synthesized as follows:

(1S-cis)-N-[[3-[[[(Carboxymethyl)amino]carbonyl]-2,2,3-
10 trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester (0.7g, 1.15mmol) is dissolved in methanol (12mL). To this is added a mixture of $LiOH \cdot H_2O$ (0.243g, 5.8mmol), aqueous H_2O_2 (30%, 2mL), and H_2O (2mL). After overnight
15 stirring, the reaction mixture is diluted with water (50mL), and evaporated (room temperature, in vacuo/ N_2 flow) until the methanol is gone. The aqueous solution is then transferred to a separatory funnel and shaken with diethyl ether (2X20mL). The aqueous
20 layer is then evaporated, to remove residual diethyl ether, and cooled in an ice water bath. The stirred solution is then brought to pH3-4 using aqueous HCl (1N). The resultant precipitate is isolated by suction filtration (with water washes) to give the
25 target compound as a white solid (0.4g, 58% yield)
 1H NMR: (300MHz, $DMSO-d_6$): δ 12.45(br.s, 1H), 10.6(s, 1H), 7.74(m, 2H), 7.57-7.44(m, 3H), 7.20(m, 2H), 4.48-

240

4.40 (m, 1H), 3.65 (m, 2H), 2.94 (m, 2H), 2.64 (m, 1H),
 2.35 (m, 1H), 1.90 (m, 1H), 1.58 (m, 1H), 1.29 (m, 1H),
 1.18 (s, 3H), 1.08 (s, 3H), 0.60 (s, 3H); IR (mull) 3124,
 3088, 3078, 1738, 1666, 1628, 1612, 1588, 1563, 1552,
 1521, 1429, 1334, 1197, 1170 cm⁻¹; MS (FAB) m/z (rel.
 intensity) 592 (M+H, 99), 595 (20), 594 (69), 593
 (41), 592 (99), 519 (25), 517 (38), 240 (55), 175
 (23), 173 (33), 109 (64); HRMS(FAB) m/z calcd for
 C₂₈H₃₁Cl₂N₃O₇ +H⁺ 592.1617, found 592.1606; Anal. Calcd
 for C₂₈H₃₁Cl₂N₃O₇ : C, 56.76; H, 5.27; N, 7.09; Found:
 C, 54.92; H, 5.41; N, 6.91; KF Water: 3.05% H₂O.

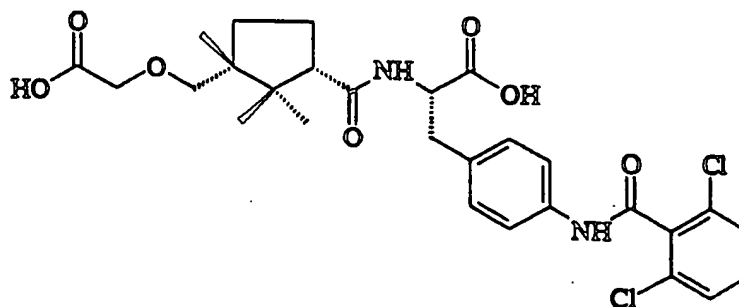
Example 182. [1S-[1 α ,3 α (E)]]-N-[[3-(2-
 Carboxyethenyl)-2,2,3-
 trimethylcyclopentyl]carbonyl]-4-[(2,6-
 dichlorobenzoyl)amino]-L-phenylalanine
 disodium salt (C₂₈H₂₈Cl₂N₂Na₂O₆).



The synthesis of Example 182 is taught by Scheme 11,
 11-G: wherein R⁴ = H, R⁵ = CO₂H
 R⁶ = 4-[(2,6-Dichlorobenzoyl)amino]-phenyl and
 Stereochemistry = [1S-[1 α ,3 α (E)]]-L. Accordingly,
 [1S-[1 α ,3 α (E)]]-N-[[3-(2-Carboxyethenyl)-2,2,3-
 trimethylcyclopentyl]carbonyl]-4-[(2,6-dichloro-
 benzoyl)amino]-L-phenylalanine disodium salt
 (C₂₈H₂₈Cl₂Na₂N₂O₆) of 11-G is synthesized as follows:
 To a solution of 11-F (R⁴ = H, R⁵ = CO₂CH₃, R⁶ = 4-[(2,6-
 Dichlorobenzoyl)amino]-phenyl, Stereochemistry = [1S-

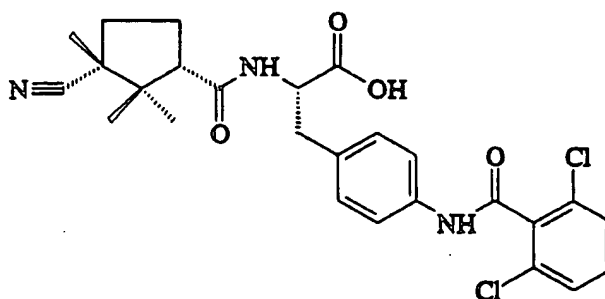
- [1 α ,3 α (E)]]-L) (0.45g, 0.78mmol) in methanol (5 mL) in a flask cooled in an ice water bath is added a solution of LiOH \cdot H $_2$ O (0.127g, 3mmol) in H $_2$ O (5mL). After two days, the mixture is diluted with water (50mL), evaporated in vacuo until the methanol is gone and then cooled to -10 $^{\circ}$ C and brought to pH 2 using 1N HCl. The resultant white precipitate is isolated by suction filtration to give a white solid which is stirred with saturated aqueous NaHCO $_3$ (2mL) and then transferred to a C-18 reversed phase HPLC column and eluted with a gradient from 0.01%aq NaHCO $_3$ to 10%acetonitrile/0.01%aq NaHCO $_3$. Evaporation in vacuo to give Example 182 as a white solid (0.25 g, 51% yield).
- 1 H NMR(300MHz, DMSO- d_6) δ 7.51-7.42(m, 5H), 7.06(m, 2H), 6.39(m, 1H), 5.49(m, 1H), 4.10(m, 1H), 2.99(m, 1H), 2.86(m, 1H), 2.56(m, 1H), 1.85(m, 2H), 1.61(m, 1H), 1.29(m, 1H), 0.90(s, 3H), 0.85(s, 3H), 0.51(s, 3H); IR (mull) 3393, 3257, 3124, 3035, 1654, 1604, 1562, 1544, 1515, 1431, 1398, 1325, 799, 778, 722cm $^{-1}$; MS (FAB) m/z (rel. intensity) 605 (M+H, 44), 629 (9), 627 (14), 608 (8), 607 (30), 606 (14), 605 (44), 585 (14), 583 (21), 73 (45), 23 (99); KF Water: 7.09% H_2O .

- 25 Example 183. (1S-cis)-N-[[3-[(Carboxymethoxy)methyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (C $_{28}$ H $_{31}$ Cl $_2$ N $_3$ O $_7$).



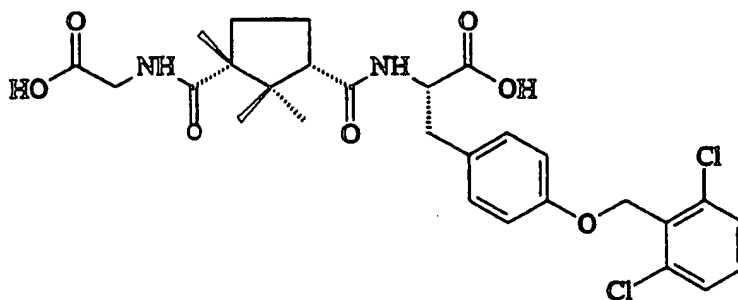
The synthesis of Example 183 is taught by Scheme 9 and by the narrative accompanying Scheme 9.

Example 184. (1*S*-*cis*)-*N*-[(3-Cyano-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine
($C_{26}H_{27}Cl_2N_3O_4$).



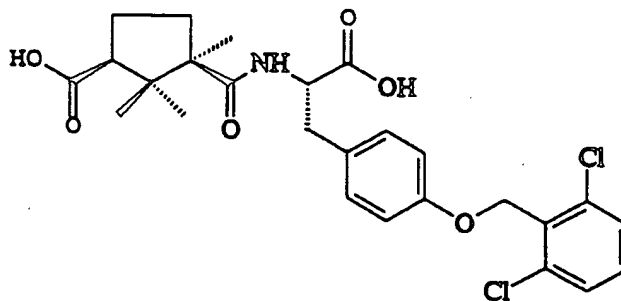
The synthesis of Example 184 is taught by Scheme 12 under the heading Preparation of Example 184.

Example 185. (1*S*-*cis*)-*N*-[[3-[[[(Carboxymethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine
($C_{28}H_{32}Cl_2N_2O_7$).



- The synthesis of Example 185 is taught by scheme 7, 7-G: wherein $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2H$, $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]-phenyl$ and Stereochemistry = (1*S*-cis) - L. Accordingly, (1*S*-cis)-N-[[3-[[[(Carboxymethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine ($C_{28}H_{32}Cl_2N_2O_7$) is prepared from 7-G-2 (7-G: $R^{7-1} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]phenyl$, Stereochemistry = (1*S*-cis)-L as like as Example 181. 1H NMR (300MHz, DMSO- d_6) δ 7.8-6.9(m, 9H), 5.18(s, 2H), 4.42(m, 1H), 3.8-3.6(m, 2H), 3.02-2.82(m, 2H), 2.65(m, 1H), 2.38(m, 1H), 1.91(m, 1H), 1.58(m, 1H), 1.30(m, 1H), 1.19(s, 3H), 1.10(s, 3H), 0.61(s, 3H); IR (mull) 3409, 1733, 1645, 1612, 1585, 1564, 1511, 1439, 1297, 1239, 1197, 1179, 1018, 786, 770 cm^{-1} ; MS (FAB) m/z (rel. intensity) 579 (M+H, 99), 582 (22), 581 (67), 580 (44), 579 (99), 578 (21), 240 (34), 161 (21), 159 (34), 109 (46), 91 (37); HRMS (FAB) calcd for $C_{28}H_{32}Cl_2N_2O_7 + H^+$ 579.1664, found 579.1667.

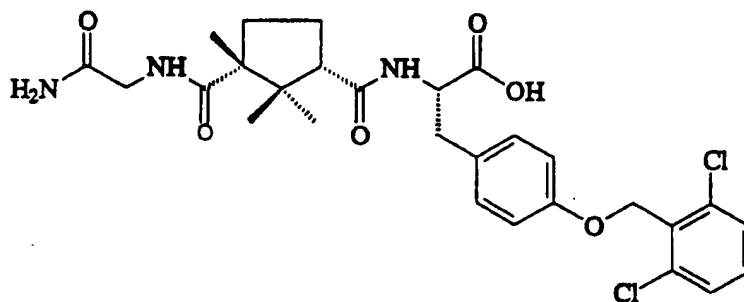
Example 186. (1*R*-cis)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine ($C_{26}H_{29}Cl_2NO_6$).



- 25 Compound IIII-a (where $R^4 = H$, $R^{5a} = CO_2CH_3$, $R^6 = 4-[(2,6-dichlorophenyl)methoxy]phenyl$, $n = 1$, Stereochemistry

S) and (1R)-camphoric anhydride were heated together in diisopropylethyl amine. The crude mixture was concentrated in vacuo to yield crude I-b (where $R^1 = H$, $R^3 = CH_3$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 =$
 5 4-[(2,6-dichlorophenyl)methoxy]phenyl, $n=1$, Stereochemistry = (1R-cis)-L). I-b was hydrolyzed with LiOH to yield **Example 186** (I-a; where $R^1 = H$, $R^3 = CH_3$, $R^4 = H$, $R^5 = CO_2H$, and $R^6 =$
 10 4-[(2,6-dichlorophenyl)methoxy]phenyl, $n=1$, Stereochemistry (1R-cis)-L): ^{13}C NMR δ 175.9, 175.4, 173.0, 158.6, 137.3, 133.0, 132.0, 131.3, 130.9, 129.7, 115.5, 65.9, 56.5, 54.2, 53.0, 47.0, 36.8, 33.1, 23.2, 22.8, 22.0, 21.0.

Example 187 (1S-cis) - N - [[3 - [[(2-Amino-2-oxoethyl)amino]carbonyl] - 2,2,3-trimethylcyclopentyl]carbonyl] - O - [(2,6-dichlorophenyl)methyl] - L-tyrosine
 15 ($C_{28}H_{33}Cl_2N_3O_6$).



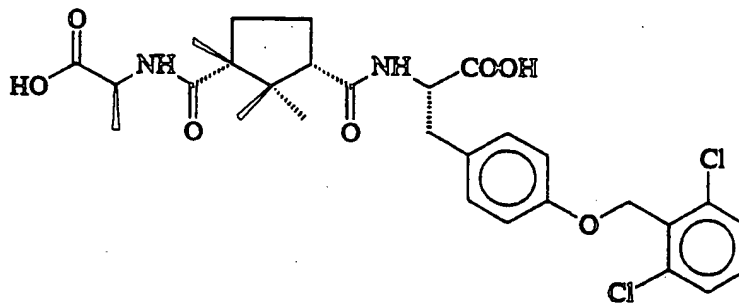
The synthesis of Example 187 is taught by Scheme 8, 8-G:
 20 wherein $R^{6-1} = H$, $R^{6-2} = H$, $R^4 = H$, $R^6 = 4-[(2,6-2,6-Dichlorophenyl)methoxy]-phenyl$
 Stereochemistry = (1S-cis) - L. Accordingly,
 (1S-cis) - N - [[3 - [[(2-Amino-2-oxoethyl)amino]carbonyl] - 2,2,3-trimethylcyclopentyl]carbonyl] - O - [(2,6-dichloro-
 25 phenyl)methyl] - L-tyrosine ($C_{28}H_{33}Cl_2N_3O_6$) is prepared from

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8-F-2 ($R^{8-1} = H$, $R^{8-2} = H$, $R^4 = H$, $R^5 = CO_2CH_3$, $R^6 = 4-[(2,6-dichlorophenyl)methoxy]-phenyl$, Stereochemistry = (1*S*-cis)-L) as taught by Scheme 8.

1H NMR(300MHz, DMSO- d_6) δ 7.74 (m, 2H), 7.55-7.40(m, 4H), 7.15(m, 3H), 6.94(m, 3H), 5.16(s, 2H), 4.41(m, 1H), 3.75-3.48(m, 2H), 3.1-2.8(m, 2H), 2.63(m, 1H), 2.33(m, 1H), 1.87(m, 1H), 1.54(m, 1H), 1.32(m, 1H), 1.17(s, 3H), 1.08(s, 3H), 0.58(s, 3H); MS (FAB) m/z (rel. intensity) 578 ($M+H$, 99), 581 (30), 580 (72), 579 (57), 578 (99), 577 (19), 504 (17), 322 (18), 239 (35), 161 (29), 159 (34); HRMS (FAB) calcd for $C_{28}H_{33}Cl_2N_3O_6 + H^+$ 578.1824, found 578.1836.

Example 188. [1*S*-[1 α ,3 α (R^*)]-N-[[3-[[[1-Carboxyethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine ($C_{29}H_{34}Cl_2N_2O_7$).

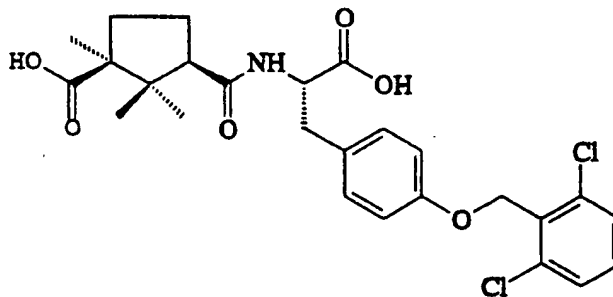


The synthesis for Example 188 is taught by scheme 7, 7-G: wherein $R^{7-1} = CH_3$, $R^4 = H$, $R^5 = CO_2H$, $R^6 = 4-[(2,6-dichlorophenyl)methoxy]-phenyl$ and Stereochemistry = [1*S*-[1 α ,3 α (R^*)]-L. Accordingly, [1*S*-[1 α ,3 α (R^*)]-N-[[3-[[[1-Carboxyethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine ($C_{29}H_{34}Cl_2N_2O_7$)

is prepared from 7-G-3 as taught by Scheme 7.

¹H NMR (300MHz, DMSO-d₆) δ 7.71 (m, 1H), 7.54-7.43 (m, 3H), 7.28 (m, 1H), 7.16 (m, 2H), 6.93 (m, 2H), 5.16 (s, 2H), 4.40 (m, 1H), 4.16 (m, 1H), 3.02-2.80 (m, 2H), 2.63 (m, 1H), 2.35 (m, 1H), 1.86 (m, 1H), 1.54 (m, 1H), 1.35-1.23 (m, 4H), 1.14 (s, 3H), 1.08 (s, 3H), 0.59 (s, 3H); IR (mull) 3427, 3031, 1731, 1645, 1612, 1585, 1565, 1512, 1439, 1297, 1239, 1230, 1197, 1179, 1017 cm⁻¹; MS (FAB) m/z (rel. intensity) 593 (M+H, 99), 596 (22), 595 (69), 594 (43), 593 (99), 592 (17), 504 (22), 254 (63), 161 (44), 159 (40), 109 (72).

Example 189. (1R-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine (C₂₆H₂₉Cl₂NO₆).



The ester III-a (R⁴ = H, R^{5a} = CO₂CH₃, R⁶ = 4-[(2,6-dichlorophenyl)methoxy]phenyl, n = 1, Stereochemistry = R) (391 mg, 1 mmol), THF (3 mL), and diisopropylethyl amine (880 μL, 5 mmol) were combined. (1S)-Camphoric anhydride (33-A) (182 mg, 1 mmol) was added and the reaction was heated at reflux for 18 h. The reaction mixture was then cooled and concentrated in vacuo. The material was treated with 1 N HCl (1 mL) and extracted with EtOAc (3 x 5 mL). The organic portion was dried and concentrated in vacuo to yield 590 mg of crude methyl ester I-a as a mixture of

regioisomers and diastereomers. Only characteristic and easily discernable protons are listed for the major product (1R-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlorophenyl)methyl]-L-tyrosine methyl ester (I-a):¹

5 H NMR (CDCl₃) δ 0.75 (s, H), 1.00 (s, H), 1.19 (s, H), 3.75 (s, H), 4.84-5.00 (m, H), 5.23 (s, H).

The crude methyl ester I-a (560 mg, 1 mmol) was combined with LiOH·H₂O (420 mg, 10 mmol) that was

10 dissolved in 6 mL of H₂O. After 4.5 h of stirring on the rotovap, 1 N HCl (12 mL) was added to the reaction mixture and a white precipitate was formed. The mixture was extracted with EtOAc (3 x 20 mL). The organic portion was dried and concentrated in vacuo to

15 afford 480 mg of crude di-acid Example 189. The material was purified by a C₁₈ reverse phase chromatography (on the Delta Prep employing a Delta-PAK C₁₈, 15 μ M particle size column that was conditioned with CH₃CN/H₂O/TFA (40:60:0.1)). The

20 material was eluted with CH₃CN/H₂O (38:62) to yield 190 mg (36% overall from anhydride) of Example 189: [α]_D -4.5° (c = 0.6, EtOH), [α]_D -2.8° (c = 0.8, EtOH); ¹H NMR (DMSO-d₆) δ 0.21 (s), 0.59 (s), 0.86 (s), 1.05-1.18 (m), 1.28-1.45 (m), 1.64-1.82 (m), 2.05-2.20 (m), 2.41 (m), 2.57 (m), 2.87 (m), 4.22-4.32 (m), 4.95 (s), 6.73 (m), 6.97 (m), 7.20-7.30 (m), 7.34 (m), 7.61 (m); ¹³C NMR (DMSO-d₆) δ 176.9 (s), 173.4 (s), 172.0 (s), 157.1 (s), 136.0 (s), 131.8 (s), 131.5 (d), 130.3 (s), 130.1 (d), 128.7 (d), 114.3 (d), 64.9 (t), 55.4 (s), 53.5 (d), 52.2 (d), 45.5 (s), 35.9 (t), 32.3 (t), 22.4 (t), 22.0 (q), 21.5 (q), 20.8 (q); IR (mineral oil mull) 3296, 2925, 1712, 1698, 1651, 1512, 1438, 1242, cm⁻¹; MS for C₂₆H₂₉Cl₂NO₆, m/z (relative intensity) 523 (M⁺, 1), 521 (M⁺, 1), 503 (1), 477 (1), 324 (29), 322 (45), 267 (19), 265 (28), 161 (64), 159 (100). Anal. Calcd for C₂₆H₂₉Cl₂NO₆: C, 59.78; H, 5.60; Cl, 13.57, N, 2.68.

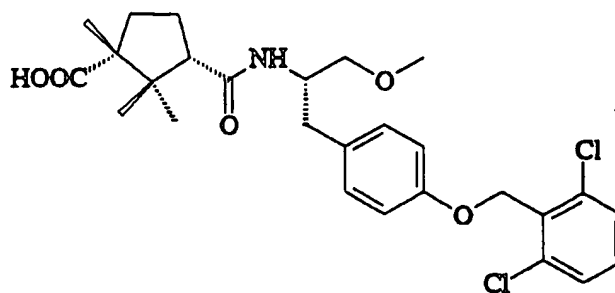
35

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Found: C, 59.41; H, 5.55; Cl, 13.43, N, 2.52.

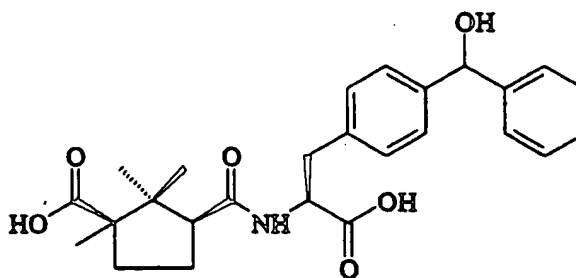
Corrected for 1.14% H₂O found by Karl Fisher analysis.

Example 190. [1S-[1 α (R'),3 α]]-N-[[3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]- α -methoxymethyl-4-[(2,6-dichlorophenyl)-methoxy]benzene-ethanamine



The synthesis of Example 190 is taught by Scheme 25.

Example 191. (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-(hydroxyphenylmethyl)-L-phenylalanine (C₂₆H₃₁NO₆).



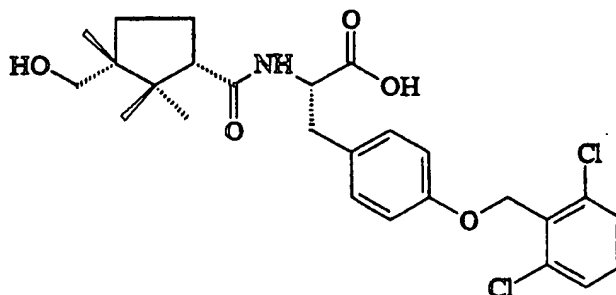
The synthesis of Example 191 is taught by scheme 2, I-c: wherein R^{2a} = -CO₂H, R¹ = Me, R³ = R⁴ = H, R⁵ = -CO₂H, R⁶ = 4-(hydroxyphenylmethyl)-phenyl, X = -C(O)- and Stereochemistry = (1S-cis)-L. Accordingly, (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)-

carbonyl]-4-(hydroxyphenylmethyl)-L-phenylalanine
(C₂₆H₃₁NO₆) is synthesized as follows:

To a solution of Example 40 (0.59 g, 1.3 mmol) in
absolute EtOH under N₂ at 0 °C is added NaBH₄ (100 mg,
5 2.7 mmol). The reaction mixture is stirred for 17 h at
room temperature diluted with H₂O, and quenched with 1
N HCl. The solution is treated with satd NH₄Cl and
adjusted to approximately pH 3 with 1 N HCl. The
mixture is extracted with EtOAc. The combined extracts
10 are dried, filtered and concentrated to give a
colorless oil (0.60 g). The product is purified by C18
reverse phase chromatography (isocratic 35:65
CH₃CN/H₂O). The product (0.29 g) is diluted with
MeOH/H₂O, frozen and lyophilized to give Example 191 as
15 a white powder: TLC R_f = 0.18 (650:350:1
CHCl₃/acetone/HCO₂H); HPLC t_R = 7.3 min (isocratic
650:350:1 CH₃CN/H₂O/TFA); [α]_D²⁵ +26° (c 0.48, MeOH); IR
(mull) 3327, 1709, 1653, 1514, 1242, 1207, 1118, 1017,
950, 700 cm⁻¹; ¹H NMR (CD₃OD) δ 7.37-7.14 (9 H), 5.73 (1
20 H), 4.90 (2 H), 4.66 (1 H), 3.20 (1 H), 2.96 (1 H),
2.70-2.62 (1 H), 2.48 (1 H), 1.92 (1 H), 1.59 (1 H),
1.40 (1 H), 1.19 (3 H), 1.18 (3 H), 0.74 (3 H); ¹³C NMR
(CD₃OD) δ 178.28, 173.84, 144.56, 142.97, 136.31,
128.84, 127.86, 126.79, 126.33, 126.31, 75.37, 56.00,
25 53.16, 46.19, 39.04, 36.69, 32.33, 22.43, 21.72,
21.04, 20.43; MS (FAB, HR) m/z 454.2234 (calcd [M +
H]⁺ 454.2229); MS (FAB) m/z 493, 454, 476, 436, 237,
226, 208, 109; Anal. C 65.54, H 6.74, N 3.12 (calcd C
68.86, H 6.89, N 3.09).

250

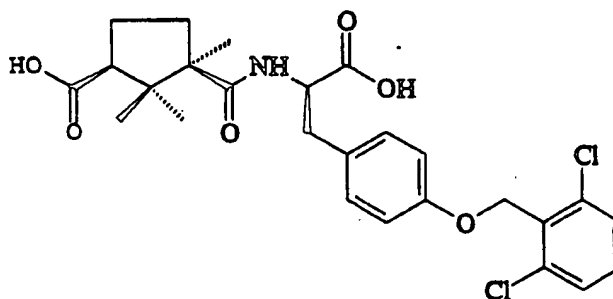
Example 192. (1*S*-*cis*)-*N*-[[3-(hydroxymethyl)-2,2,3-trimethylcyclopentyl]carbonyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine ($C_{26}H_{31}Cl_2NO_5$).



5 The synthesis of Example 192 is taught by Scheme 10 under the heading Preparation of Example 192.

Example 193. (1*R*-*cis*)-*N*-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-*O*-(2,6-dichlorophenyl)methyl]-*D*-tyrosine ($C_{26}H_{29}Cl_2NO_6$).

10



MeOH (10 mL) was cooled to 0°C and acetyl chloride (2.14 mL, 30 mmol) was added slowly. After 20 min the t-BOC-D-tyrosine derivative III-a (where $R^4 = H$, $R^{5a} = CO_2CH_3$, $R^6 = 4-[(2,6-dichlorophenyl)methoxy]phenyl$, $n=1$, Stereochemistry = R), (2.64 g, 6 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum to

15

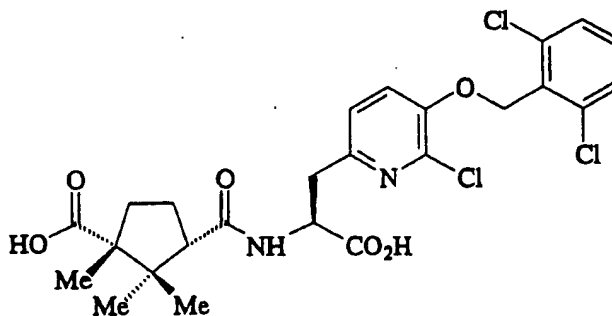
afford a white solid. The white solid was triturated with Et₂O and filtered. The solid was returned to the flask and was combined with THF (15 mL), diisopropylethyl amine (4.4 mL, 25 mmol), and (1R)-camphoric anhydride (1.0 g, 5 mmol). The reaction mixture was heated at reflux for 18 h. The mixture was then cooled and concentrated in vacuo. The material was treated with 1 N HCl (40 mL) and extracted with EtOAc (3 x 20 mL). The organic portion was dried and concentrated in vacuo to yield 3.30 g of crude methyl ester I-a as a mixture of regioisomers and diastereomers.

The crude methyl ester I-a (2.79 g, 5 mmol) was combined with LiOH·H₂O (2.1 g, 50 mmol) that was dissolved in 30 mL of H₂O. After 4.0 h of stirring on the rotovap, 1 N HCl (60 mL) was added to the reaction and a white precipitate formed. The mixture was extracted with EtOAc (3 x 40 mL). The organic portion was dried and concentrated in vacuo to afford 3.05 g of crude di-acid. The material was chromatographed on 150 g of silica gel eluting with CHCl₃/EtOAc/HCO₂H (50:50:0.1) to yield pure (1R-cis)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-O-(2,6-dichlorophenyl)methyl]-D-tyrosine (Example 193). This material was dissolved in 20 mL of CH₃CN/H₂O (1:1). The mixture was concentrated in vacuo until the liquid appeared milky. The solution was frozen and lyophilized to afford Example 193: ¹H NMR (DMSO-d₆) δ 0.55 (H), 1.13 (H), 1.25 (H), 1.30-1.45 (1 H), 1.68-1.86 (1 H), 1.95-2.122 (1 H), 2.25-2.41 (1H), 2.73, 2.95-3.20, 4.49-4.62, 5.23, 7.01, 7.25, 7.30-7.40, 7.45-7.70; ¹³C NMR (DMSO-d₆) δ 175.3 (s), 174.5 (s), 173.5 (s), 157.3 (s), 136.3 (s), 132.0 (d), 131.7 (s), 130.9 (s), 130.5 (d), 129.0 (d), 114.4 (d), 65.1 (t), 55.3 (s), 53.6 (d), 52.2 (d), 46.3 (s), 35.6 (t), 32.1 (t), 23.2 (q), 22.2 (t), 21.4 (q), 20.6 (q); IR

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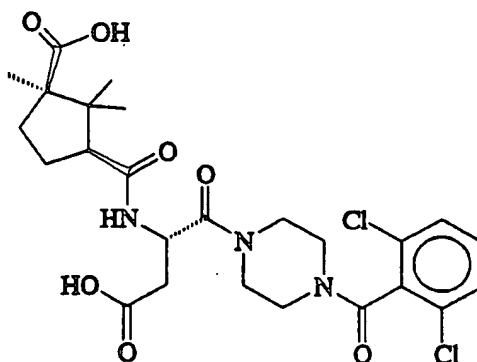
(mineral oil mull) 3436, 2922, 1722, 1707, 1634, 1612, 1512, 1438, 1242, cm^{-1} ; MS for $\text{C}_{26}\text{H}_{29}\text{Cl}_2\text{NO}_6$, m/z (relative intensity) 523 (M^+ , 0.4), 521 (M^+ , 0.5), 505 (2), 503 (2), 324 (33), 322 (50), 267 (21), 265 (32), 161 (69), 159 (100). Anal. Calcd for $\text{C}_{26}\text{H}_{29}\text{Cl}_2\text{NO}_6$: C, 59.78; H, 5.60; Cl, 13.57, N, 2.68. Found: C, 59.52; H, 5.29; Cl, 13.60, N, 2.52. Corrected for 0.9% H_2O found by Karl Fisher analysis.

10 Example 194 [1S-[1 α (R*),3 α]]- α -[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-6-chloro-5-[(2,6-dichlorophenyl)methoxy]-2-pyridinepropanoic acid



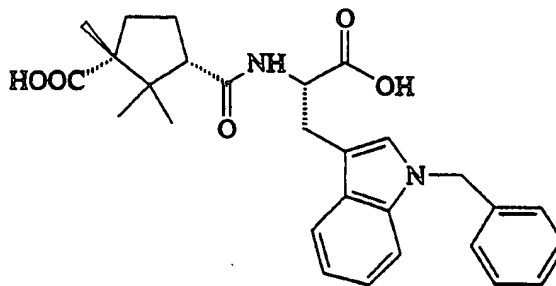
The synthesis of Example 194 is taught by Scheme 34.

Example 195 [1*S*-[1 α (*R**),3 α]]- β -[[[3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-4-(2,6-dichlorobenzoyl)- γ -oxo-1-piperazinebutanoic acid



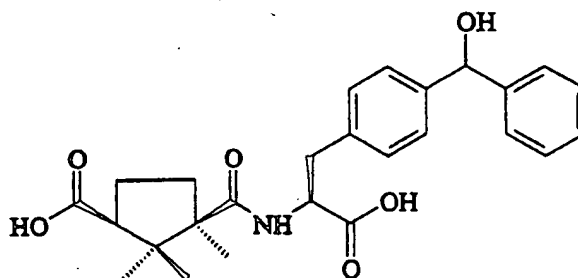
5 The synthesis of Example 195 is taught by Scheme 18.

Example 196. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-1-(phenylmethyl)-*L*-tryptophan (C₂₈H₃₂N₂O₅).



Example 196 was synthesized as described Scheme 24.

Example 197. [1R-cis]-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-4-(hydroxyphenylmethyl)-L-phenylalanine ($C_{26}H_{31}NO_6$).

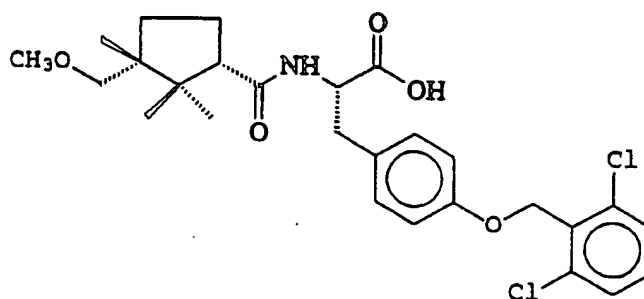


- 5 The synthesis of Example 197 is taught by scheme 2, I-c: wherein $R^{2a} = -CO_2H$, $R^1 = R^4 = H$, $R^3 = Me$, $R^5 = -CO_2H$, $R^6 = 4-(hydroxyphenylmethyl)-phenyl$, $X = -C(O)-$ and Stereochemistry = (1R-cis)-L. Accordingly, [1R-cis]-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)-
- 10 carbonyl]-4-(hydroxyphenylmethyl)-L-phenylalanine ($C_{26}H_{31}NO_6$) is prepared from 32-B and (1R)-camphoric anhydride by the procedures taught by Scheme 2 and by the synthesis of Examples 40, 186, and 191: TLC silica gel $R_f = 0.31$ (900:100:1 $CHCl_3/MeOH/HCO_2H$); HPLC $t_R =$
- 15 5.6 min (isocratic 650:350:1 $CH_3CN/H_2O/TFA$); $[\alpha]_D^{25} +24^\circ$ (c 0.38, MeOH); UV (MeOH) λ_{max} (ϵ) 223 (14200), 254 (425 sh), 258 (493), 263 (481), 268 (364 sh), 272 (257 sh); IR (mull) 3379, 1712, 1642, 1514, 1417, 1377, 1342, 1274, 1179, 1133, 1017, 700 cm^{-1} ; 1H NMR (CD_3OD) δ
- 20 7.35-7.15 (m 9H), 5.73 (1 H), 4.91 (3 H), 4.72 (1 H), 3.26 (1 H), 2.99 (1 H), 2.72 (1 H), 2.44-2.30 (1 H), 2.15-2.00 (1 H), 1.82-1.67 (1 H), 1.40-1.27 (1 H), 1.05 (3 H), 1.03 (3 H), 0.54 (3 H), 0.53 (3 H); ^{13}C NMR (CD_3OD) δ 176.29, 176.24, 173.56, 144.56, 143.17,
- 25 136.26, 136.23, 128.82, 127.88, 126.85, 126.39, 126.31, 75.33, 55.77, 53.34, 52.47, 46.20, 36.09, 32.03, 22.11, 21.98, 20.17, 20.07; MS (HR FAB) m/z 454.2230 (calcd $[M+H]^+$ 454.2229); MS (FAB) m/z 454,

255

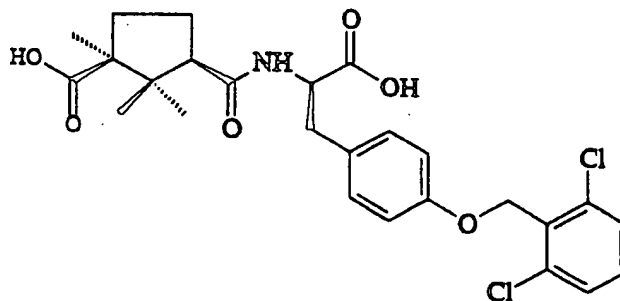
436, 237, 226, 208, 109; H₂O (Karl Fischer) 1.44%;
Anal. C 67.68, H 6.98, N 3.06 (calcd adjusted for H₂O:
C 68.86, H 6.89, N 3.09).

5 Example 198. (1*S*-*cis*)-*N*-[[[(3-methoxymethyl)-2,2,3-trimethylcyclopentyl]carbonyl]-*O*-[(2,6-dichlorophenyl)methyl]-*L*-tyrosine
(C₂₇H₃₃Cl₂NO₃).



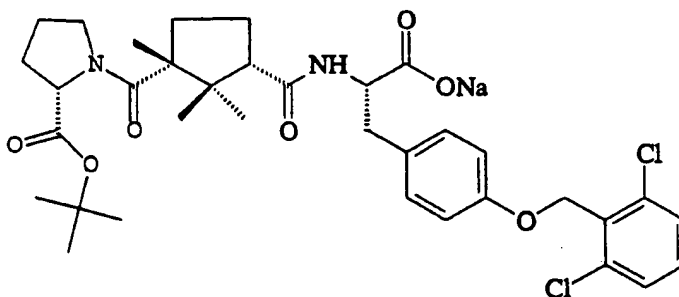
The synthesis of Example 198 is taught by Scheme 10 under the heading Preparation of Example 198.

10 Example 199. (1*R*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-[(2,6-dichlorophenyl)methyl]-*D*-tyrosine
(C₂₆H₂₉Cl₂NO₄).



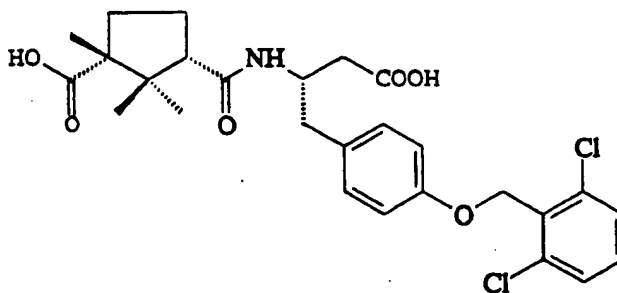
In the same manner as the synthesis of 189, 199 was synthesized and purified (0.5 g, 49% overall yield): $[\alpha]_D = -31^\circ$.

Example 200. [1R-[1 α ,3 α (S*)]]-N-[[3-[[[1-Carboxy-2-
5 [4-[(2,6-
dichlorophenyl)methoxy]phenyl]ethyl]-
amino]carbonyl]-1,2,2-
trimethylcyclopentyl]carbonyl]-L-
proline 1,1-dimethylethyl ester,
10 monosodium salt (C₃₅H₄₃Cl₂N₂NaO₇).



The synthesis of Example 200 is taught by Scheme 21.

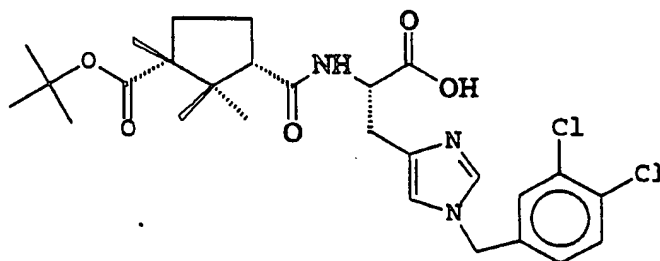
Example 201. [1S-[1 α (R*),3 α]]- β -[[3-Carboxy-2,2,3-
15 trimethylcyclopentyl]carbonyl]amino]-4-
[(2,6-dichlorophenyl)methoxy]-
benzenebutanoic acid (C₂₇H₃₁Cl₂NO₆).



The synthesis of Example 201 is taught by scheme 2, I-c: wherein $R^2 = -CO_2H$, $R^1 = Me$, $R^3 = R^4 = H$, $R^5 = -CH_2CO_2H$, $R^6 = 4-[(2,6-Dichlorophenyl)methoxy]-phenyl-$, $n = 1$, Stereochemistry = $[1S-[1\alpha(R^*),3\alpha]]$.

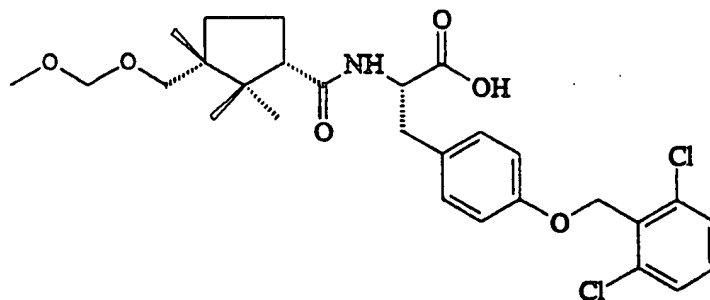
- 5 Accordingly, $[1S-[1\alpha(R^*),3\alpha]]-\beta-[[[3-Carboxy-2,2,3-trimethylcyclopentyl]carbonyl]amino]-4-[(2,6-dichlorophenyl)methoxy]-benzenebutanoic acid (C_{27}H_{31}Cl_2NO_6)$ is prepared from 30-B and 15-D as taught by Scheme 2: TLC: $R_f = 0.22$ (50:50:0.2 hexanes/EtOAc/HCO₂H); $[\alpha]_D =$
 10 $+3$ (MeOH); IR 3320, 3057, 3026, 2953, 2924, 2868, 2855, 1703, 1641, 1612, 1585, 1565, 1511, 1465, 1439, 1403, 1378, 1297, 1283, 1241, 1197, 1179, 1158, 1017, 768 cm⁻¹; ¹H NMR δ 0.71 (3 H), 1.22 (3 H), 1.23 (3 H), 1.41-1.53 (1 H), 1.67-1.86 (1 H), 2.26-2.60 (4 H),
 15 2.71-2.87 (2 H), 2.96-3.08 (1 H), 4.46-4.62 (1 H), 5.26 (2 H), 5.43 (1 H), 6.98 (2 H), 7.13 (2 H), 7.23-7.28 (1 H), 7.37 (2 H); ¹³C NMR δ 20.22, 21.66, 22.29, 22.91, 31.91, 37.19, 39.64, 46.44, 48.57, 54.26, 56.48, 65.14, 115.09, 128.37, 129.62, 130.23,
 20 130.33, 131.98, 136.90, 157.72, 171.75, 178.54, 182.19; MS (FAB) m/z 536, 495, 464, 449, 431, 418, 386, 353, 336, 287, 236; H₂O (Karl Fischer) 0.70%; Anal. C 60.08, H 5.86, Cl 13.05, N 2.70 (calcd corrected for H₂O: C 60.03, H 5.86, Cl 13.13, N 2.59).

- 25 Example 202. (1S-cis)-1-[(3,4-Dichlorophenyl)methyl]-N-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-L-histidine (C₂₇H₃₅Cl₂N₃O₅).



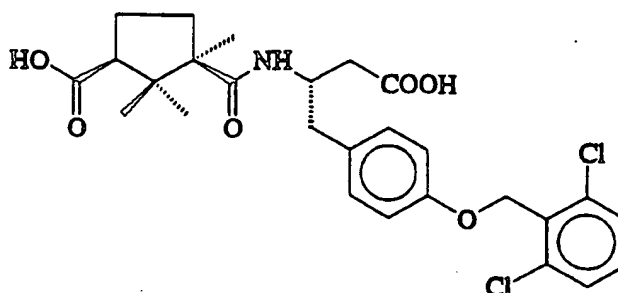
To (1S-cis)-N-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-1-[(3,4-dichlorophenyl)methyl]-L-histidine methyl ester (0.5 g, 0.88 mmol) in H₂O (10 mL) was added
 5 LiOH·H₂O (10 equiv, 8.8 mmol, 0.37 g) in cold H₂O (10 mL). Stirred reaction overnight. Lowered pH of reaction solution to 5 with 1N HCl. Filtered resulting precipitate, washed precipitate with H₂O and dried precipitate under hi vacuum conditions to yield
 10 0.46 g (95%) of (1S-cis)-1-[(3,4-Dichlorophenyl)methyl]-N-[[3-[(1,1-dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-L-histidine **Example 202** (I-c; where R^{2a} = (1,1-dimethylethoxy)carbonyl, R¹ =
 15 CH₃, R³ = H R⁴ = H, R⁵ = CO₂H, and R⁶ = 1-[(3,4-dichlorophenyl)methyl]-4-imidazolyl, n = 1, Stereochemistry = (1S-cis)-L): mp 234-235°C.

Example 203. (1S-cis)-N-[[3-(3-Methoxymethoxymethyl)-2,2,3-trimethylcyclopentyl]carbonyl]-O-
 20 [(2,6-dichlorophenyl)methyl]-L-tyrosine (C₂₇H₃₃Cl₂NO₅).



The synthesis of Example 203 is taught by Scheme 10 under the heading Preparation of Example 203.

Example 204. [1R-[1 α (S[°]),3 α]]- β -[[[3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]amino]-4-[(2,6-dichlorophenyl)methoxy]-benzenebutanoic acid (C₂₇H₃₁Cl₂NO₆).

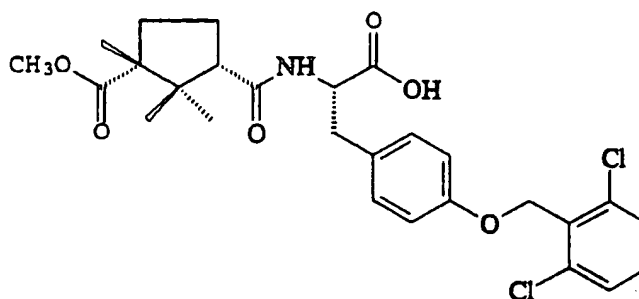


- 5 The synthesis of Example 204 is taught by scheme 2, I-c: wherein R^{2a} = -CO₂H, R¹ = R⁴ = H, R³ = Me, R⁵ = -CH₂CO₂H, R⁶ = 4-[(2,6-Dichlorophenyl)methoxy]phenyl-, n = 1, Stereochemistry = [1R-[1 α (S[°]),3 α]]. Accordingly, [1R-[1 α (S[°]),3 α]]- β -[[[3-Carboxy-1,2,2-
- 10 trimethylcyclopentyl)carbonyl]amino]-4-[(2,6-dichlorophenyl)methoxy]benzenebutanoic acid (C₂₇H₃₁Cl₂NO₆) is obtained from 30-B and (1S)-camphoric anhydride (33-A) by the procedures taught by Scheme 1: mp 106-108°C; TLC R_f = 0.24 (250:250:1
- 15 hexanes/EtOAc/HCO₂H); [α]_D = +13 (MeOH); IR 3144, 3057, 3030, 2954, 2924, 2870, 2855, 1706, 1627, 1612, 1585, 1565, 1511, 1466, 1439, 1377, 1299, 1241, 1197, 1178, 1017, 1000, 778, 768 cm⁻¹; ¹H NMR δ 0.70 (3 H), 1.16 (3 H), 1.16 (3 H), 1.30 (3 H), 1.43-1.61 (1 H),
- 20 1.77-1.97 (1 H), 2.09-2.32 (2 H), 2.36-2.49 (1 H), 2.57-2.68 (1 H), 2.69-2.83 (2 H), 2.90-3.02 (1 H), 4.44-4.59 (1 H), 5.25 (2 H), 5.73 (1 H), 6.97 (2 H), 7.11 (2 H), 7.22-7.26 (3 H), 7.37 (2 H); ¹³C NMR δ 20.88, 21.16, 22.04, 23.15, 32.57, 37.76, 39.59,
- 25 47.39, 48.16, 52.44, 55.73, 65.17, 86.13, 115.02, 128.37, 129.56, 130.34, 132.00, 136.89, 157.72, 174.53, 178.42, 181.12; MS (FAB) m/z 536, 518, 490, 378, 354, 336, 294, 159, 137, 109, 88, 69, 55; H₂O

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(Karl Fischer) 0.52%; Anal. C 60.07, H 5.84, Cl 13.03, N 2.71 (calcd corrected for H₂O: C 60.14, H 5.85, Cl 13.15, N 2.60).

Example 205. (1*S*-cis)-O-[(2,6-Dichlorophenyl)methyl]-N-[(3-(methoxycarbonyl)-2,2,3-trimethylcyclopentyl)carbonyl]-L-tyrosine (C₂₇H₃₁Cl₂NO₆).



Example 205 is taught by Scheme 20, 20-D: wherein R⁴ = H, R⁵ = CO₂H, R⁶ = 4-[(2,6-Dichlorophenyl)methoxy]-phenyl and Stereochemistry = [1*S*-cis]-L.

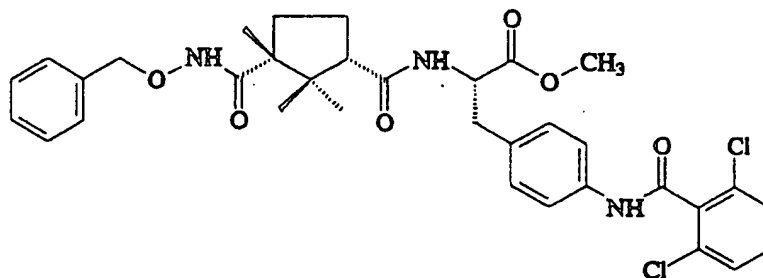
To a solution of the diester 20-D (R⁴ = H, R⁵ = CO₂CH₃; R⁶ = 4-[(2,6-Dichlorophenyl)methoxy]phenyl, Stereochemistry = (1*S*-cis)-L (0.32g, 0.58mmol) in methanol (5mL) is added a solution of LiOH·H₂O (0.31g, 7.4mmol) in H₂O (5mL). After overnight stirring, the mixture is diluted with water (50mL) and evaporated in vacuo until the methanol is gone. The aqueous solution is cooled in an ice bath and brought to pH4 using 1N HCl, resulting in a white precipitate which is chromatographed on silica gel (10% methanol/chloroform) to give a white solid (0.25g, 80% yield).

¹H NMR(D₂O) 7.85(m, 1H), 7.58-7.44(m, 3H), 7.19(m, 2H), 6.96(m, 2H), 5.18(s, 2H), 4.43(m, 1H), 3.59(s, 3H), 3.03-2.81(m, 2H), 2.69(m, 1H), 2.40(m, 1H), 1.91(m, 1H), 1.56(m, 1H), 1.39(m, 1H), 1.16(s, 3H),

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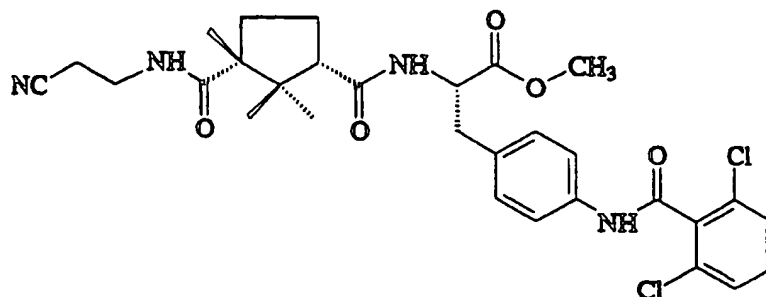
1.31(s, 3H), 0.59(s, 3H); IR (mull) 1727, 1639, 1612, 1585, 1565, 1511, 1439, 1298, 1241, 1197, 1179, 1160, 1119, 779, 768; MS (FAB) m/z (rel. intensity) 536 (M+H, 99), 538 (66), 537 (39), 536 (99), 322 (22), 197 (27), 169 (21), 159 (29), 137 (31), 109 (66), 107 (22).

Example 206 (1*S*-*cis*)-4-[(2,6-Dichlorobenzoyl)amino]-*N*-[[2,2,3-trimethyl-3-[(phenylmethoxy)amino]carbonyl]cyclopentyl]carbonyl]-*L*-phenylalanine methyl ester (C₃₄H₃₇Cl₂N₃O₆).



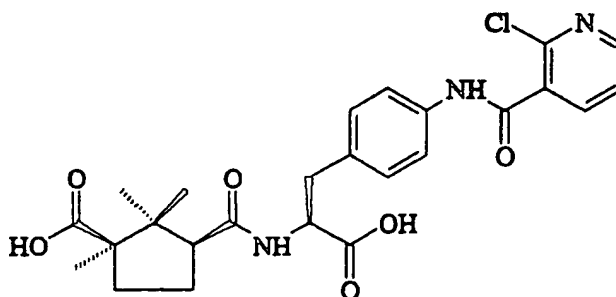
The synthesis of Example 206 is taught by Scheme 23 under the heading Preparation 23-C.

Example 207 (1*S*-*cis*)-*N*-[[3-[(2--Cyanoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine methyl ester



The synthesis of Example 207 is taught by Scheme 22 under the heading Preparation of 22-C.

Example 208. (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2-chloro-3-pyridinyl)carbonyl]amino]-L-phenylalanine ($C_{25}H_{28}ClN_3O_6$).

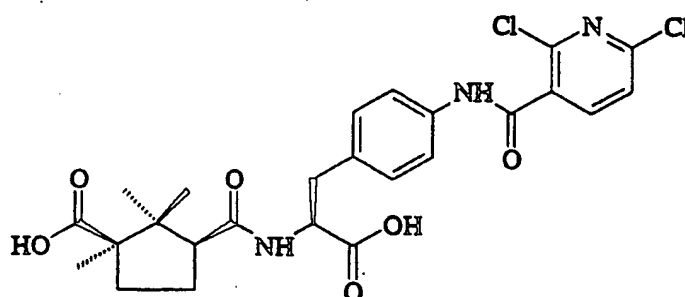


The synthesis of Example 208 is taught by Scheme 2, I-c: wherein $R^{2a} = -CO_2H$, $R^1 = Me$, $R^3 = R^4 = H$, $R^5 = -CO_2H$, $R^6 = 4-[[[(2-chloro-3-pyridyl)-$
 10 carbonyl]amino]phenyl, $n = 1$, Stereochemistry = (1*S*-cis)-L. Accordingly, (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2-chloro-3-pyridinyl)carbonyl]amino]-L-phenylalanine ($C_{25}H_{28}ClN_3O_6$) is prepared from 31-C, 15-D and 2-chloro-3-nicotinic
 15 acid by the procedures taught by Scheme 2: mp 172-174 °C; TLC silica gel $R_f = 0.17$ (750:250:3 EtOAc/hexanes/ HCO_2H); IR (mineral oil mull) 3410, 3289, 3193, 3124, 3050, 2955, 2924, 2868, 2855, 1714, 1655, 1606, 1582, 1537, 1516, 1461, 1415, 1401, 1377, 1329,
 20 1279, 1257, 1242, 1207, 1187, 1152 cm^{-1} ; 1H NMR δ 0.80 (3 H), 1.13-1.28 (1 H), 1.16 (3 H), 1.19 (3 H), 1.38-1.50 (1 H), 1.67-1.83 (1 H), 2.08-2.23 (1 H), 2.45-2.58 (2 H), 3.04-3.24 (2 H), 4.75-4.87 (1 H), 5.96 (1 H), 7.12 (2 H), 7.32 (1 H), 7.56 (2 H), 7.96
 25 (1 H), 8.43 (1 H), 9.32 (1 H); MS (FAB) m/z 504, 502, 484, 468, 456, 371, 320, 302, 274, 140, 109; Anal. C

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57.54, H 5.84, Cl 6.79, N 8.05 (calcd corrected for H₂O: C 57.55, H 5.83, Cl 6.79, N, 8.08).

Example 209 (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-
 5 [[(2,6-dichloro-3-pyridinyl)carbonyl]amino]-*L*-phenylalanine (C₂₅H₂₇Cl₂N₃O₆).

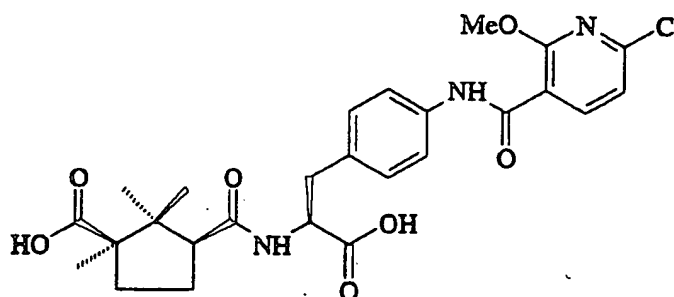


The synthesis of Example 209 is taught by Scheme 2, I-c: wherein R^{2a} = -CO₂H, R¹ = Me, R³ = R⁴ = H, R⁵ =
 10 -CO₂H, R⁶ = 4-[(2,6-dichloro-3-pyridyl)-carbonyl]amino]phenyl, n = 1, Stereochemistry = (1*S*-*cis*)-*L*. Accordingly, (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[2,6-dichloro-3-pyridinyl)carbonyl]amino]-*L*-phenylalanine
 15 (C₂₅H₂₇Cl₂N₃O₆) is prepared from 31-C, 15-D and 2,6-dichloro-3-nicotinic acid as taught by Scheme 2 and by the synthesis of Example 208: mp 246-247 °C; TLC silica gel R_f = 0.28 (750:250:2 EtOAc/hexanes/HCO₂H); IR (mineral oil mull) 3292, 3196,
 20 3125, 3059, 2954, 2923, 2855, 1712, 1656, 1607, 1575, 1544, 1515, 1461, 1426, 1414, 1377, 1343, 1329, 1272, 1244, 1206, 1186, 1160, 1144 cm⁻¹; ¹H NMR δ 0.65 (3 H), 1.10 (3 H), 1.15 (3 H), 1.24-1.37 (1 H), 1.43-1.62 (1 H), 1.83-1.97 (1 H), 2.26-2.45 (1 H), 2.67 (1 H),
 25 2.82-3.04 (2 H), 3.30 (3 H), 4.38-4.49 (1 H), 7.21 (2

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H), 7.55 (2 H), 7.71 (1 H), 7.80 (1 H), 8.14 (1 H), 10.63 (1 H); MS (FAB) m/z 538, 536, 538, 518, 490, 371, 354, 336, 281, 200, 174, 137, 109.

Example 210. (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2-methoxy-6-chloropyridin-3-yl)carbonyl]-amino]-*L*-phenylalanine



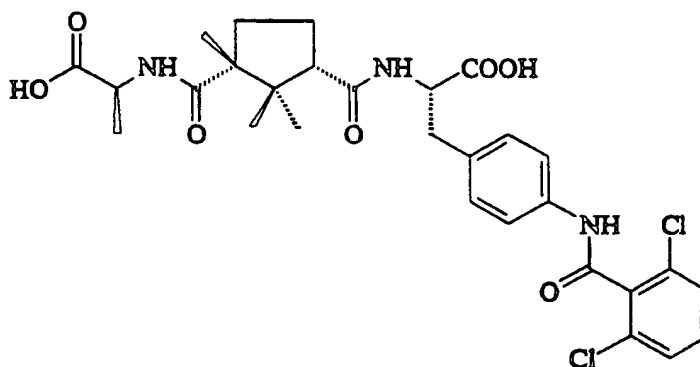
The synthesis of Example 210 is taught by Scheme 2, I-c: wherein $R^{2a} = -CO_2H$, $R^1 = Me$, $R^3 = R^4 = H$, $R^5 = -CO_2H$, $R^6 = 4-[[[(6-chloro-2-methoxy-3-pyridyl)-carbonyl]amino]phenyl$, $n = 1$, Stereochemistry = (1*S*-*cis*)-*L*. Accordingly, Example 210 is synthesized as follows:

A solution of the dimethyl ester of Example 209 (0.098 g, 0.18 mmol) in 4:1 THF/MeOH is reacted at room temperature under Ar with an aqueous solution of $LiOH \cdot H_2O$ (0.042 g, 1.0 mmol). The reaction mixture is stirred for 2.5 h. It is diluted with H_2O , acidified with aq HCl, and extracted with EtOAc. The combined extracts are washed with brine, dried, filtered and concentrated to an oil that is purified by silica gel flash chromatography (650:350:4 EtOAc/hexanes/ HCO_2H). The product is azeotroped thrice from toluene, diluted with CH_3CN/H_2O , and lyophilized to give 0.043 g (0.081 mmol, 45%) of Example 210 as a white solid: mp 128-131

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°C; TLC silica gel R_f = 0.13 (500:500:2 EtOAc/hexanes/HCO₂H); ¹H NMR δ 0.64 (3 H), 1.10 (3 H), 1.15 (3 H), 1.23-1.38 (1 H), 1.44-1.53 (m, 1 H), 1.78-1.97 (m, 1 H), 2.66 (t, 2 H, J = 9.4), 2.78-3.07 (m, 2 H), 3.67-3.84 (1 H), 3.96 (3 H), 4.37-4.46 (1 H), 7.19 (2 H), 7.57 (2 H), 7.78 (2 H), 8.05 (1 H), 10.18 (1 H); MS (FAB) m/z 534, 532, 514, 486, 371, 360, 350, 332, 304, 275, 190, 127, 109.

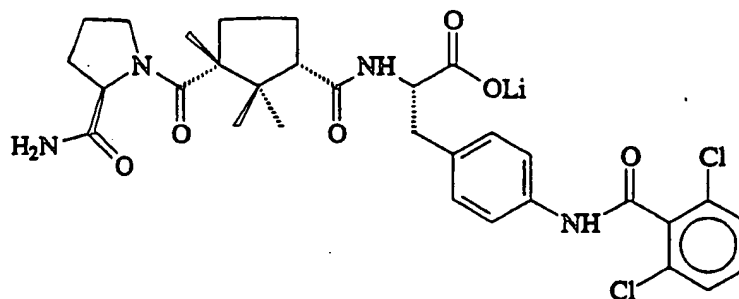
Example 211. [1*S*-[1 α ,3 α (*R*^{*})]]-*N*-[[[3-[[[1-Carboxyethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine



The synthesis of Example 211 is taught by Scheme 19 under the heading Preparation of Example 211.

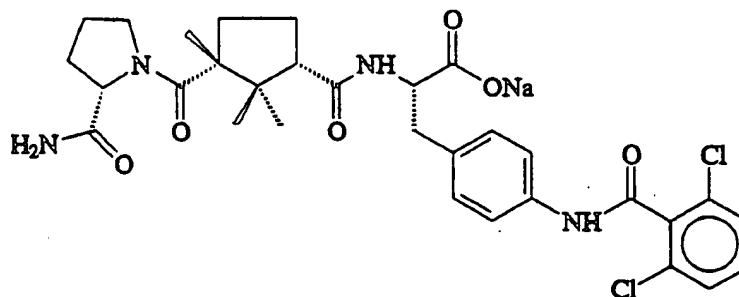
Example 212. [1*S*-[1 α ,3 α (*S*^{*})]]-*N*-[3-[[2-(Aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine monolithium salt

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The synthesis of Example 212 is taught by Scheme 19 under the heading Preparation of Example 212.

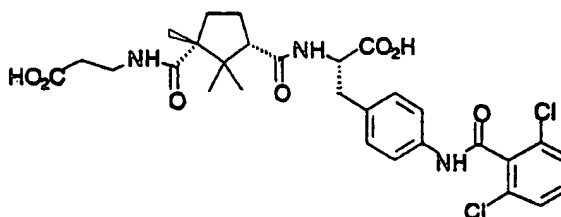
Example 213. [1*S*-[1 α ,3 α (*R*^{*})]]-*N*-[3-[[2-(Aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine monosodium salt



The synthesis of Example 213 is taught by Scheme 19 under the heading Preparation of Example 213.

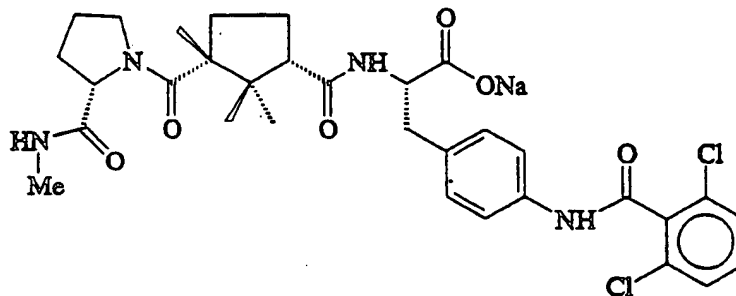
Example 214 (1*S*-*cis*)-*N*-[[3-[[2-Carboxyethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine (C₂₉H₃₃Cl₂N₃O₇).

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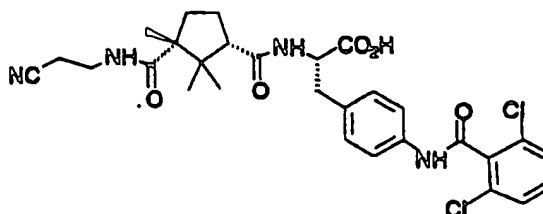
The synthesis for Example 214 is taught by Scheme 19 under the heading Preparation of Example 214.

Example 215 [1S-[1 α ,3 α (R*)]]-N-[3-[[2-((Methylamino)carbonyl)-1-pyrrolidinyl]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine monosodium salt



The synthesis for Example 215 is taught by Scheme 19 under the heading Preparation of Example 215.

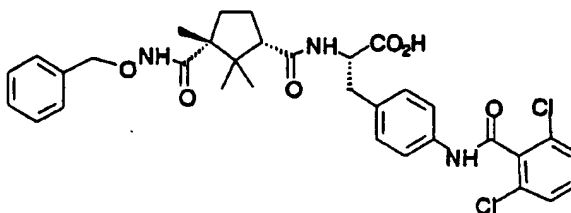
Example 216 (1S-cis)-N-[[3-[[2-(Cyanoethyl)-amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine



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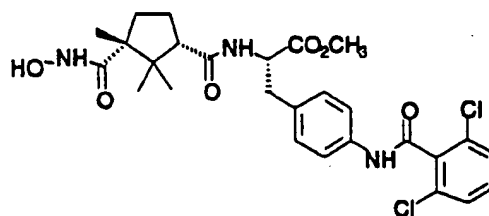
The synthesis of Example 216 is taught by Scheme 22 under the heading Preparation of Example 216.

- 5 Example 217 (1*S*-*cis*)-4-[(2,6-Dichlorobenzoyl)amino]-*N*-[[2,2,3-trimethyl-3-[[[(phenylmethoxy)amino]carbonyl]cyclopentyl]carbonyl]-*L*-phenylalanine ($C_{33}H_{35}Cl_2N_3O_6$).



The synthesis for Example 217 is taught by Scheme 23 under the heading Preparation of Example 217.

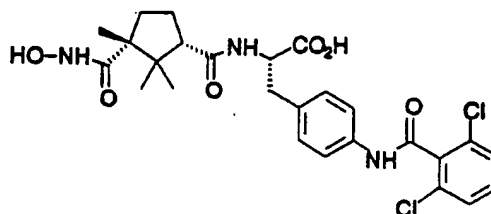
- 10 Example 218 (1*S*-*cis*)-4-[(2,6-Dichlorobenzoyl)amino]-*N*-[[3-[(hydroxyamino)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-*L*-phenylalanine methyl ester.



- 15 The synthesis for Example 218 is taught by Scheme 23 under the heading Preparation of Example 218.

Example 219 (1*S*-*cis*)-4-[(2,6-Dichlorobenzoyl)amino]-*N*-[[3-[(hydroxyamino)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-*L*-phenylalanine

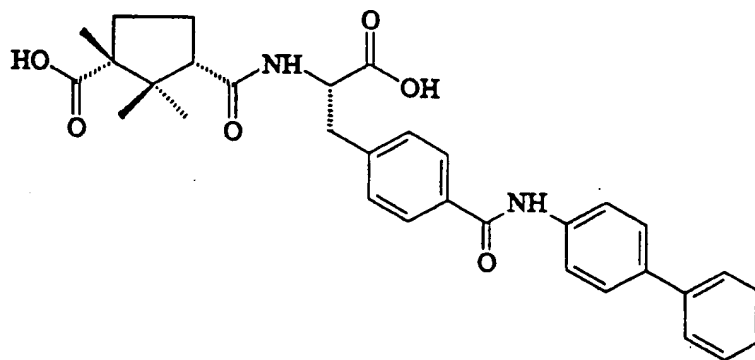
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The synthesis for Example 219 is taught by Scheme 22 under the heading Preparation of Example 219.

Example 220 (1*S*-*cis*)-*N*-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(1,1'-biphenyl)-4-yl]amino]carbonyl]-*L*-phenylalanine

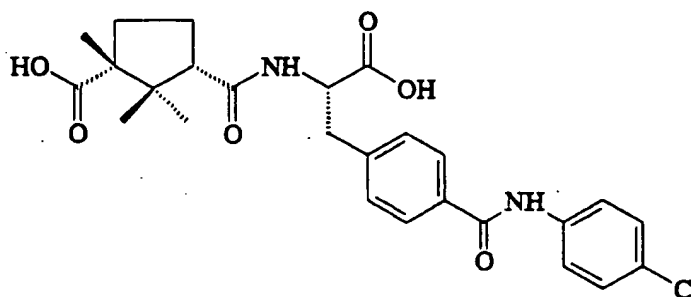
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The synthesis for Example 220 is taught by Schemes 35 and 2 under the heading Preparation of Example 220.

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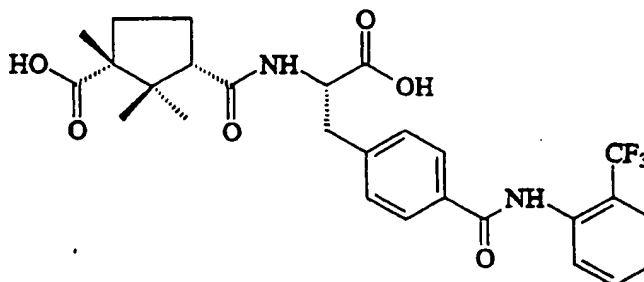
Example 221 (1*S*-cis)-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(4-chlorophenyl)amino]carbonyl]]-L-phenylalanine



5 The synthesis for Example 221 is taught by Schemes 35 and 2 under the heading Preparation of Example 221.

Example 222 (1*S*-cis)-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2-trifluoromethylphenyl)amino]carbonyl]]-L-phenylalanine

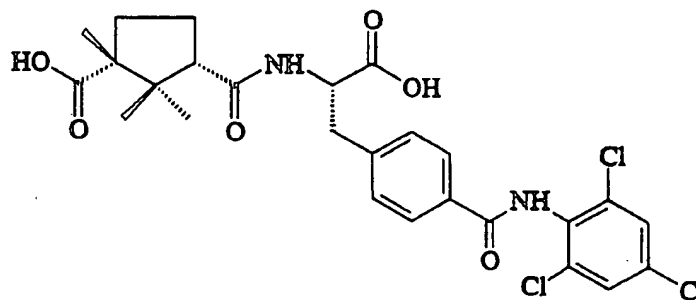
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The synthesis for Example 222 is taught by Schemes 35 and 2 under the heading Preparation of Example 222.

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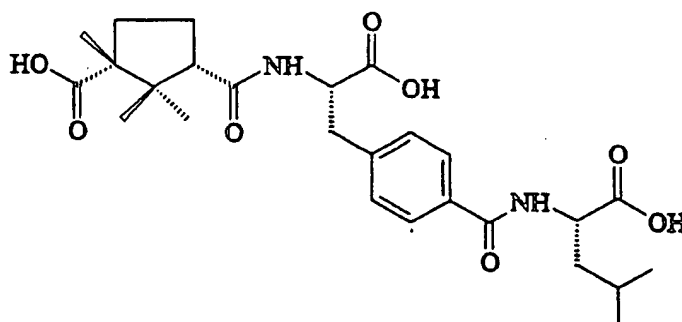
Example 223 (1*S*-*cis*)-[[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2,4,6-trichlorophenyl)amino]carbonyl]-L-phenylalanine



5 The synthesis for Example 223 is taught by Schemes 35 and 2 under the heading Preparation of Example 223.

Example 224 [1*S*-[1 α (*R**),3 α]]-4-[[[(1-Carboxy-3-methylbutyl)amino]carbonyl]-*N*-[[[(3-carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-L-phenylalanine

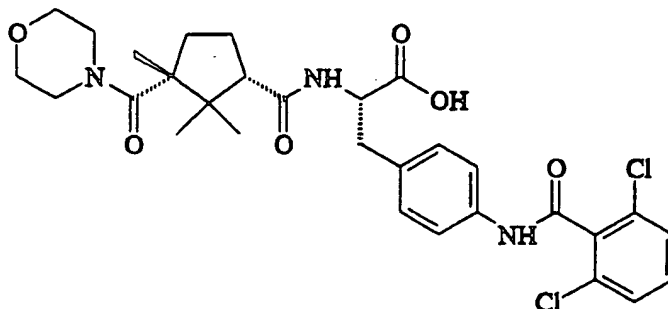
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The synthesis for Example 224 is taught by Schemes 35 and 2 under the heading Preparation of Example 224.

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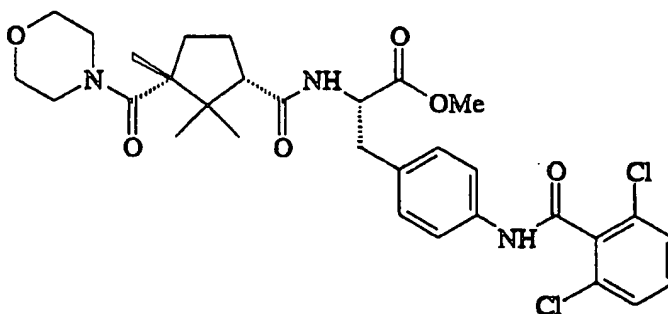
Example 225 (1*S*-cis)-4-[(2,6-Dichlorobenzoyl)amino]-*N*-[[2,2,3-trimethyl-3-[(4-morpholinyl)carbonyl]cyclopentyl]carbonyl]-*L*-phenylalanine



5 The preparation of Example 225 is taught by Scheme 27.

Example 226 (1*S*-cis)-4-[(2,6-Dichlorobenzoyl)amino]-*N*-[[2,2,3-trimethyl-3-[(4-morpholinyl)carbonyl]cyclopentyl]carbonyl]-*L*-phenylalanine methyl ester

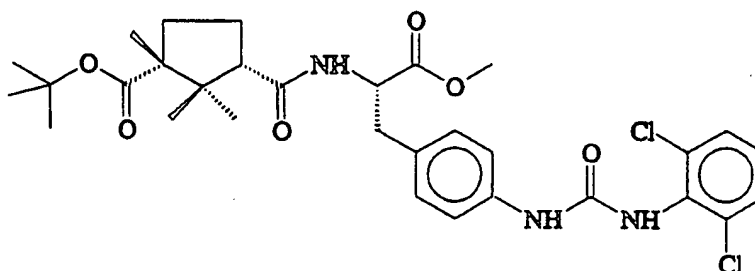
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The preparation of Example 226 is taught by Scheme 27.

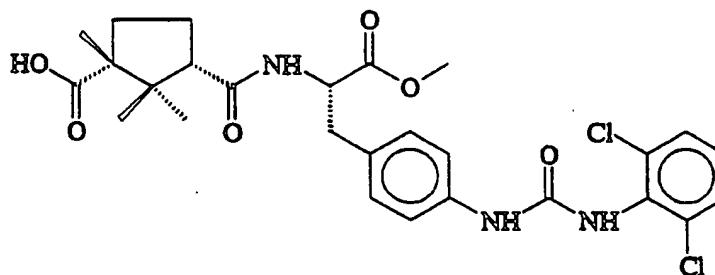
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Example 227 (1*S*-*cis*)-*N*-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[[[(2,6-dichlorophenyl)amino]carbonyl]amino]-*L*-phenylalanine methyl ester



The synthesis of Example 227 is taught by Scheme 26.

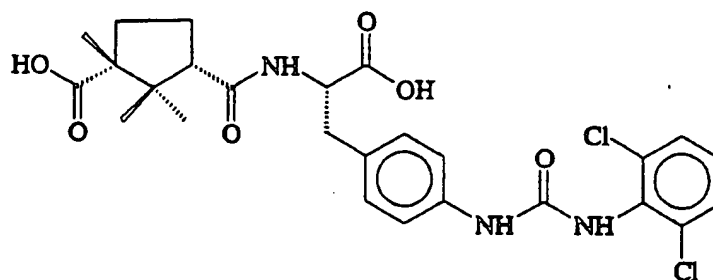
Example 228 (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2,6-dichlorophenyl)amino]carbonyl]amino]-*L*-phenylalanine methyl ester



The synthesis of Example 228 is taught by Scheme 26.

Example 229 (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[[(2,6-dichlorophenyl)amino]carbonyl]amino]-*L*-phenylalanine

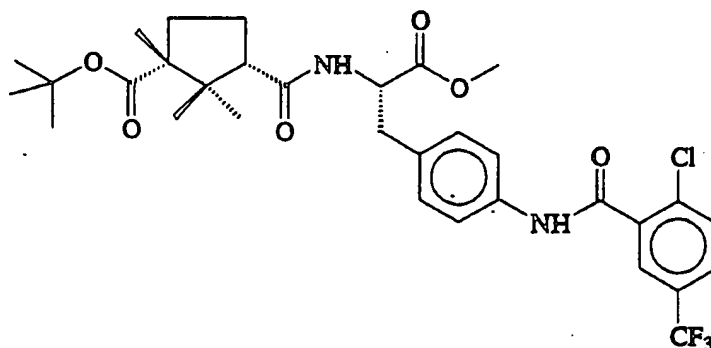
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The synthesis of Example 229 is taught by Scheme 26.

Example 230 (1S-cis)-N-[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2-chloro-5-trifluoromethylbenzoyl)amino]-L-phenylalanine methyl ester

5

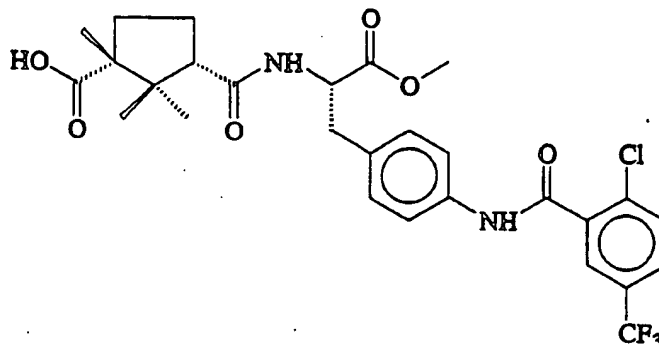


Example is 230 synthesized in the same manner as Example 54.

Example 231 (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2-chloro-5-trifluoromethylbenzoyl)amino]-L-phenylalanine methyl ester

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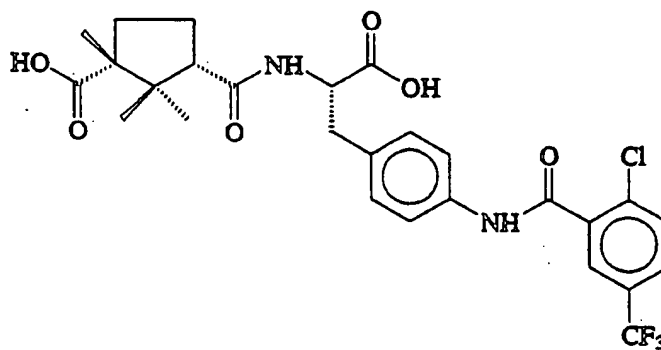
275



Example 231 is synthesized in the same manner as Example 54.

Example 232 (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2-chloro-5-trifluoromethylbenzoyl)amino]-L-phenylalanine

5

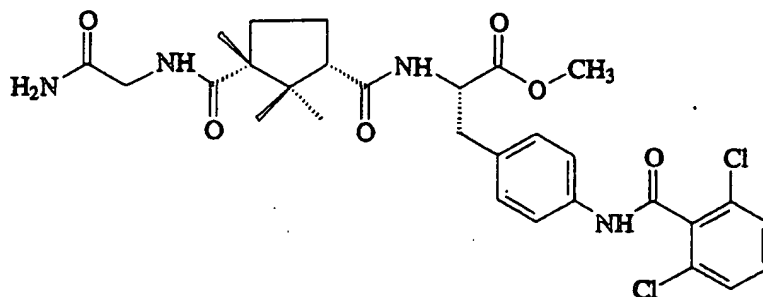


Example 232 is synthesized in the same manner as Example 54.

Example 233 (1S-cis)-N-[[3-[[[(2-Amino-2-oxoethyl)amino]carbonyl]-2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester

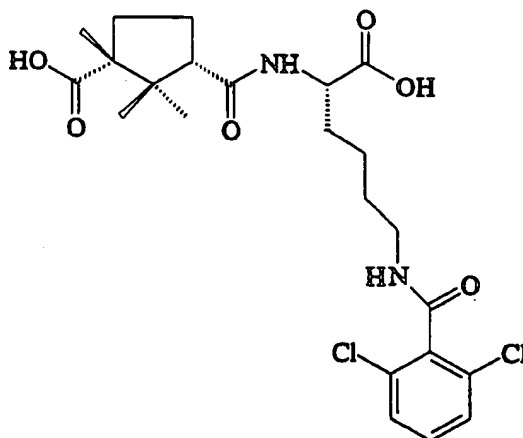
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The synthesis for Example 233 is taught by Scheme 8 under the heading Preparation of 8-F.

Example 234 [1S-[1 α (R^{*}),3 α]]-2-[[[3-Carboxy-2,2,3-trimethylcyclopentyl]carbonyl]amino]-6-
 5 [(2,6-dichlorobenzoyl)amino] hexanoic acid



Example 234 was prepared according to Scheme 2.

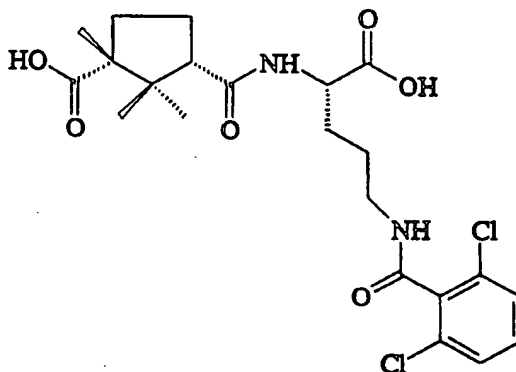
Physical properties as follows: ¹H NMR

(300 MHz, CD₃OD) δ 7.36 (3 H), 4.29 (1 H), 3.24 (2 H),
 10 2.71 (1 H), 2.45 (1 H), 2.04 (1 H), 1.71 (8 H), 1.23
 (3 H), 1.13 (3 H), 0.75 (3 H); ¹³C NMR (75 MHz, CD₃OD) δ
 176.74, 173.06, 164.47, 137.20, 131.64, 130.84,
 128.05, 55.91, 52.87, 46.16, 38.50, 32.31, 30.44,

277

28.43, 22.64, 22.32, 21.92, 21.07, 20.57; MS (FAB) m/z (rel. intensity) 501 (M^+ , 22), 504 (20), 503 (32), 502 (26), 501 (22), 109 (17), 73 (99), 69 (25), 57 (27), 55 (23); MS (ES-) for $C_{23}H_{30}Cl_2N_2O_6$ m/z 499.3 ($M-H$); Anal. Calcd for $C_{23}H_{30}Cl_2N_2O_6 \cdot 0.25 H_2O$: C, 54.60; H, 6.07; N, 5.53. Found: C, 54.58; H, 6.14; N, 5.45.

Example 235 [1S-[1 α (R'), 3 α]]-2-[[[3-Carboxy-2,2,3-trimethylcyclopentyl]carbonyl]amino]-5-[(2,6-dichlorobenzoyl)amino] pentanoic acid



Example 235 was prepared according to Scheme 2.

Physical properties as follows: 1H NMR

(300 MHz, CD_3OD) δ 7.38 (3 H), 4.41 (1 H), 3.40 (2 H), 2.83 (1 H), 2.53 (1 H), 2.08 (1 H), 1.79 (3 H), 1.47

(1 H), 1.30 (3 H), 1.24 (3 H), 0.83 (3 H); ^{13}C NMR

(75 MHz, CD_3OD) δ 178.23, 174.24, 173.83, 165.84, 136.07, 131.79, 130.67, 127.80, 56.06, 52.92, 52.10, 38.84, 32.35, 28.57, 25.43, 22.33, 21.61, 20.95,

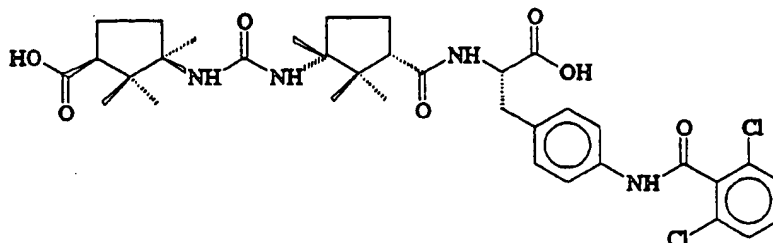
20.50; MS (FAB) m/z (rel. intensity) 487 (M^+ , 99),

490 (14), 489 (67), 488 (25), 487 (99), 305 (19), 242 (16), 175 (12), 173 (18); Anal. Calcd for $C_{22}H_{28}Cl_2N_2O_6$:

C, 54.22; H, 5.79; N, 5.75. Found: C, 53.91; H, 5.93; N, 5.43.

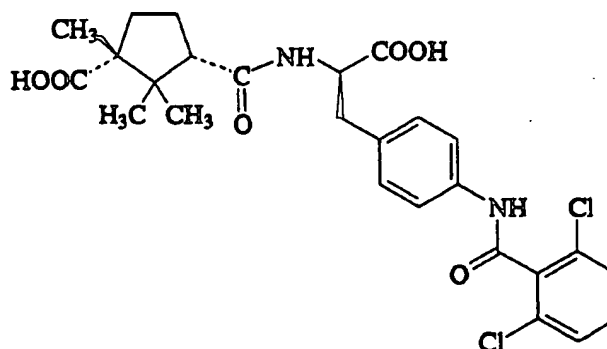
278

Example 236 [1S- [1 α , 3 α (1S', 3R')]] -N- [[3- [[[3-
Carboxy-1, 2, 2-
trimethylcyclopentyl) amino] carbonyl] -
amino] -2, 2, 3-
5 trimethylcyclopentyl] carbonyl] -4- [(2, 6-
dichlorobenzoyl) -amino] -L-phenylalanine



The synthesis of Example 236 is taught by Schemes 28 and 29.

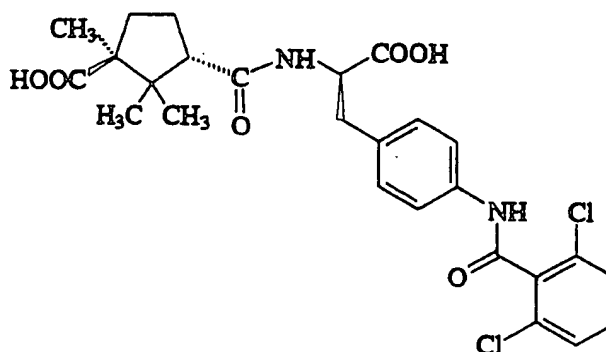
Example 237 (1S-cis) -N- [(3-Carboxy-2, 2, 3-
10 trimethylcyclopentyl) carbonyl] -4- [(2, 6-
dichlorobenzoyl) amino] -D-
phenylalanine (C₂₆H₂₈Cl₂N₂O₆)



The synthesis for Example 237 is taught by Scheme 37 under the heading Preparation of Example 237.

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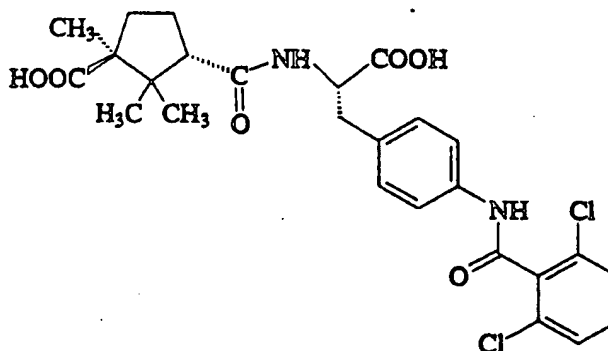
Example 238 (1S-trans)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)



5 The synthesis for Example 238 is taught by Scheme 37 under the heading Preparation of Example 238.

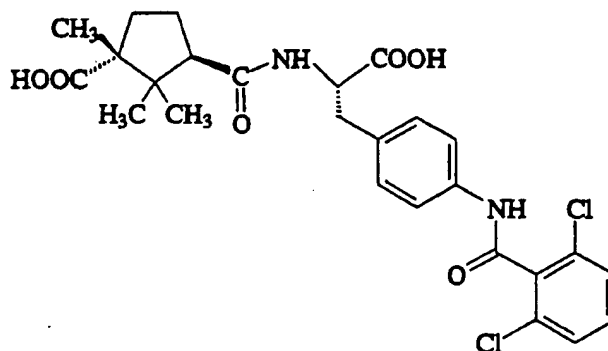
Example 239 (1S-trans)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)

10



The synthesis for Example 239 is taught by Scheme 37 under the heading Preparation of Example 239.

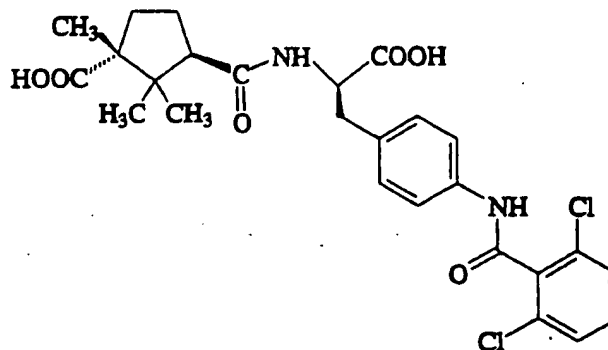
Example 240 (1R-trans)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)



5 The synthesis of Example 240 is taught by Scheme 37 under the heading Preparation of Example 240.

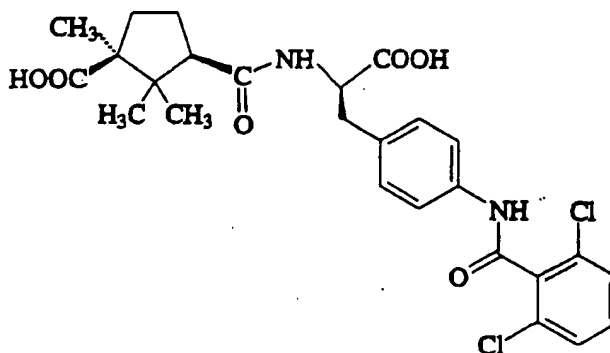
Example 241 (1R-trans)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)

10

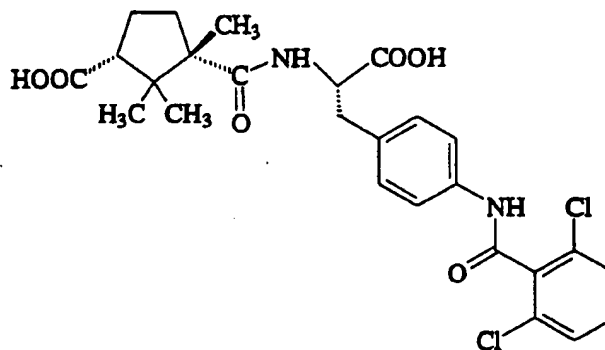


The synthesis of Example 241 is taught by Scheme 37 under the heading Preparation of Example 241.

Example 242 (1R-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl) carbonyl]-4-[(2,6-dichlorobenzoyl) amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)



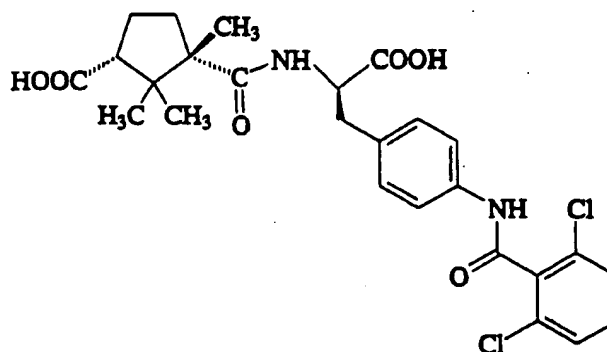
Example 244 (1S-cis)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)



5 The synthesis of Example 244 is taught by Scheme 37 under the heading Preparation of Example 244.

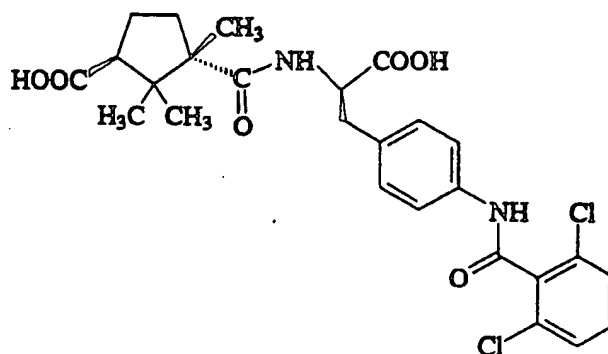
Example 245 (1S-cis)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)

10



The synthesis of Example 245 is taught by Scheme 37 under the heading Preparation of Example 245.

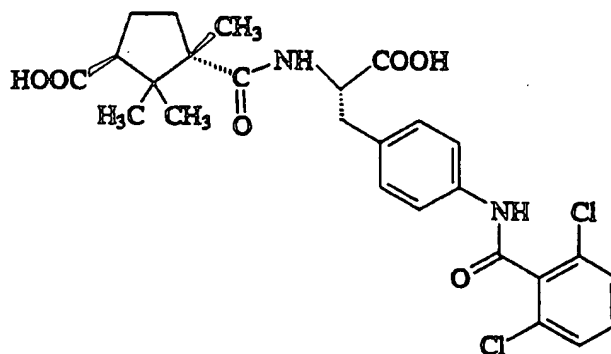
Example 246 (1S-trans)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl) carbonyl]-4-[(2,6-dichlorobenzoyl) amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)



5 The synthesis of Example 246 is taught by Scheme 37 under the heading Preparation of Example 246.

Example 247 (1S-trans)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl) carbonyl]-4-[(2,6-dichlorobenzoyl) amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)

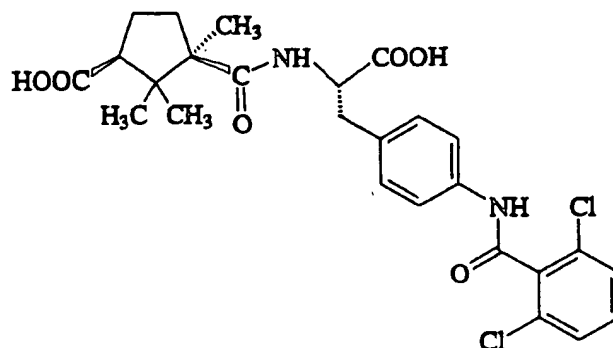
10



The synthesis of Example 247 is taught by Scheme 37 under the heading Preparation of Example 247.

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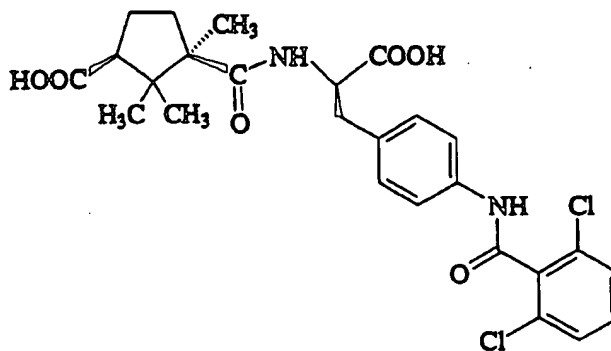
Example 248 (1R-cis)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)



5 The synthesis of Example 248 is taught by Scheme 37 under the heading Preparation of Example 248.

Example 249 (1R-cis)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)

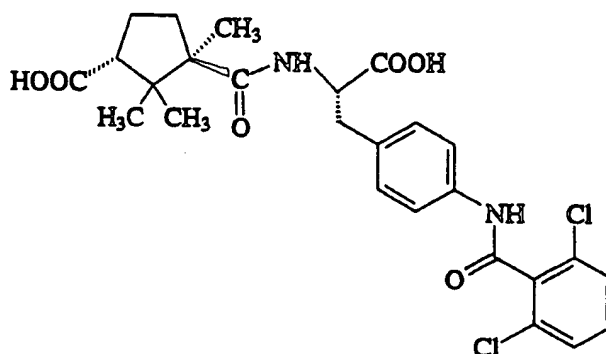
10



The synthesis of Example 249 is taught by Scheme 37 under the heading Preparation of Example 249.

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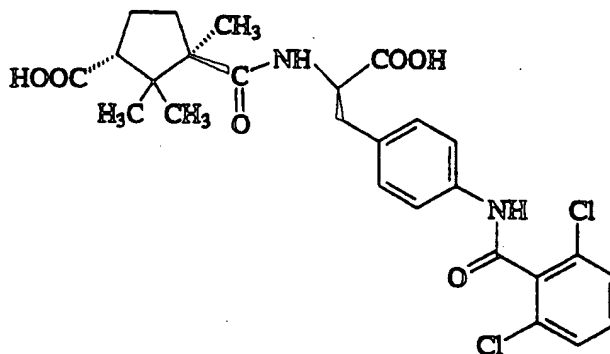
Example 250 (1R-trans)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)



5 The synthesis of Example 250 is taught by Scheme 37 under the heading Preparation of Example 250.

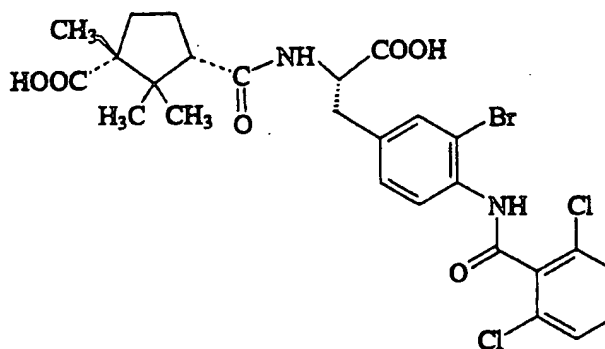
Example 251 (1R-trans)-N-[(3-Carboxy-1,2,2-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-D-phenylalanine ($C_{26}H_{28}Cl_2N_2O_6$)

10



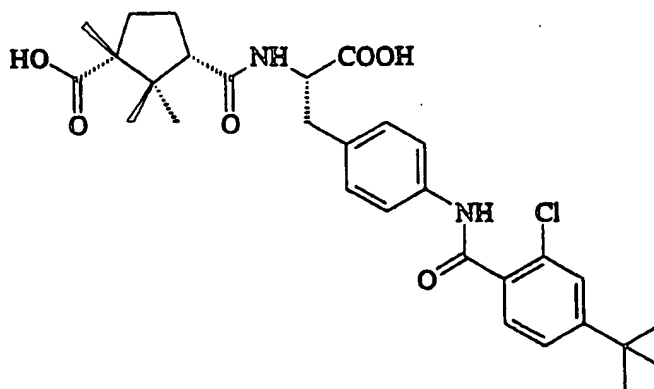
The synthesis of Example 251 is taught by Scheme 37 under the heading Preparation of Example 251.

Example 252 (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-3-bromo-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine (C₂₆H₂₈Cl₂N₂O₆)



5 The synthesis for Example 252 is taught by Scheme 2 (Method B) and is explained under the heading Preparation of Example 252.

10 Example 253 (1*S*-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[2-chloro-4-[(1,1-dimethyl)ethyl]benzoyl]amino]-L-phenylalanine (C₃₀H₃₇ClN₂O₆)

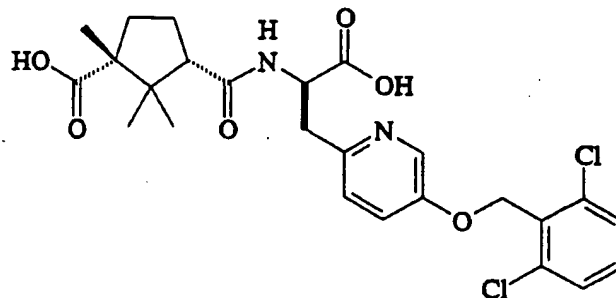


The synthesis of Example 253 is taught by Scheme 38 under the heading Preparation of Example 253.

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Example 254 [1S-[1 α (R*),3 α]]- α -[[[3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]amino]-3-[(2,6-dichlorophenyl)methoxy]-6-pyridinepropionic acid (C₂₅H₂₈Cl₂N₂O₆)

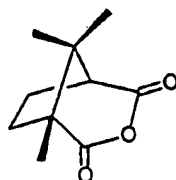
5



The synthesis of Example 254 is taught by Scheme 39 under the heading Preparation of Example 254.

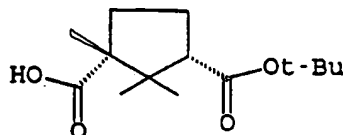
Reference Examples (R. Examples)

R. Example 1. (1R)-1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octane-2,4-dione [(1R)-camphoric anhydride]



- 5 Method A: A mixture of (1R-cis)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid [(1R,3S)-camphoric acid] (40.0 g), AcCl (23.5 g), and Ac₂O (81.6 g) was heated under reflux for 3 hr. The mixture was concentrated in vacuo, dissolved in CHCl₃, washed with
- 10 sat. NaHCO₃, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the residue was triturated with i-Pr₂O to give (1R)-1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octane-2,4-dione [(1R)-camphoric anhydride (34.0 g) as crystals.
- 15 Method B: DIEA (8.0 g) was added to a suspension of (1R,3S)-camphoric acid (5.0 g) and BOP Reagent (11.1 g) in THF (50 ml) at room temperature. The mixture was stirred for 4 hr. and the solvent was removed in vacuo. The residue was extracted with
- 20 AcOEt and the extract was washed with 5% HCl, sat. NaHCO₃, and sat. LiCl, and dried over Na₂SO₄. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (eluent; CHCl₃) to give (1R)-camphoric anhydride (4.1
- 25 g) as a colorless powder.

R. Example 2. (1*R*-*cis*)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid 3-(1,1-dimethylethyl) ester.



To a solution of (1*R*)-camphoric anhydride (0.18 g) in THF (2 ml) was added 1M *t*-BuOK in THF (1 ml) at -78°C under N₂ and the mixture was stirred for 10 hr. at the same temperature. The mixture was concentrated in vacuo, dissolved in H₂O, and extracted with AcOEt. The aqueous layer was acidified with 1N HCl to pH 3 and extracted with CH₂Cl₂. The extract was washed with brine and dried over Na₂SO₄. The solvent was removed in vacuo to give (1*R*-*cis*)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid 3-dimethylethyl ester (0.24 g).

R. Example 3. (1*R*-*cis*)-3-Formyl-1,2,2-trimethylcyclopentanecarboxylic acid.



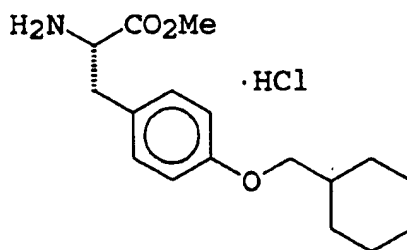
A mixture of (1*R*)-camphoric anhydride (1.76 g), *N*,*O*-dimethylhydroxylamine hydrochloride (1.13 g), DIEA (8.4 ml) in THF (15 ml) was heated for 3 hr. at 85°C in a sealed tube. After cooling, the tube was opened and 1N HCl (75 ml) was added. The resulting mixture was extracted with AcOEt.

The extract was dried over Na₂SO₄ and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel to give (1*R*,3*S*)-3-

(N-methoxy-N-methylcarbamoyl)-1,2,2-trimethylcyclopentanecarboxylic acid (800 mg).

To a solution of the obtained compound (215 mg) in THF (5 ml) was added a 1M solution of LiAlH_4 in THF (1.5 ml) at -78°C . The mixture was stirred for 1 hr. at -78°C , warmed to 0°C and quenched with 1N HCl. The resulting mixture was extracted with AcOEt. The extract was dried over Na_2SO_4 and the solvent was removed in vacuo to give a 3:1 mixture of (1R-cis)-3-Formyl-1,2,2-trimethylcyclopentanecarboxylic acid (aldehyde form) and (1R,5S)-4-hydroxy-1,8,8-trimethyl-3-oxabicyclo [3.2.1]-octane-2-one (acetal form) (153 mg). Both forms are exchangeable with each other in solution.

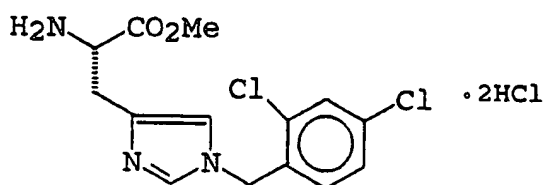
- 15 R. Example 4. O-(Cyclohexylmethyl)-L-tyrosine methyl ester, hydrochloride salt.



To a mixture of N-(tert-butoxycarbonyl)-L-tyrosine methyl ester (356 mg), K_2CO_3 (830 mg), $n\text{-Bu}_4\text{NI}$ (89 mg) in DMF (5 ml) was added cyclohexylmethyl bromide (202 μl) and the mixture was stirred for 1 day at room temperature. After addition of brine (40 ml), the resulting mixture was extracted with AcOEt. The extract was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent; 9:1, Hexane/AcOEt \rightarrow 1:1, Hexane/AcOEt) to give N-(tert-butoxycarbonyl)-O-cyclohexylmethyl-L-tyrosine methyl ester (470 mg). The obtained compound (347 mg) was

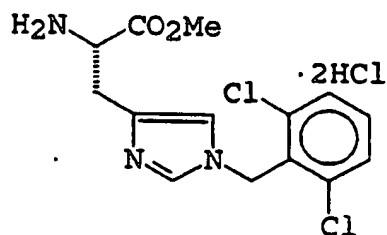
dissolved in 3N HCl/AcOEt (5 ml) and the mixture was stirred overnight. The solvent and excess HCl was removed in vacuo to give O-(Cyclohexylmethyl)-L-tyrosine methyl ester, hydrochloride salt.

- 5 R. Example 5. 1-[(2,4-Dichlorophenyl)methyl]-L-histidine methyl ester, dihydrochloride salt.



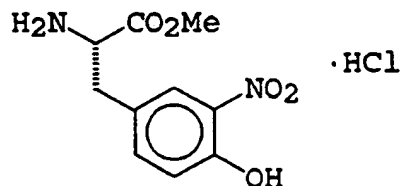
- N-(tert-butoxycarbonyl)-L-histidine methyl ester (1.0 g) was added to a solution of 2,4-dichlorobenzyl chloride (0.73 g) and Et₃N (0.27 g) in benzene (10 ml) and the mixture was heated under reflux for 1 hr. The mixture was cooled and the precipitate was removed by filtration. The filtrate was washed with H₂O, dried over Na₂SO₄, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent; 95:5, CHCl₃/MeOH) to give N-(tert-butoxycarbonyl)-1-[(2,4-dichlorophenyl)methyl]-L-histidine methyl ester. The obtained compound was treated in a similar manner as described in R. Example 4 to give 1-[(2,4-Dichlorophenyl)methyl]-L-histidine methyl ester, dihydrochloride salt.

- R. Example 6. 1-[(2,6-Dichlorophenyl)methyl]-L-histidine methyl ester, dihydrochloride salt.



L-histidine (3.13 g) was added to a solution of NaNH_2 in liquid ammonia prepared from Na (0.93 g) and FeCl_3 (catalytic amount) in liquid ammonia (50 ml). After 15 min., a solution of 2,6-dichlorobenzylchloride (3.96 g) in THF (5 ml) was added and the mixture was stirred for 3 hr. The reaction mixture was quenched with H_2O and ether. The pH of the aqueous layer was adjusted to pH 8 with 5% HCl followed by cooling. The resulting precipitate was collected by filtration, washed with H_2O , and dried to give 1-[(2,6-dichlorophenyl)methyl]-L-histidine (3.58 g). The obtained compound (0.80 g) was dissolved in MeOH (30 ml) and HCl gas was bubbled for 10 min. at 0°C . The reaction mixture was stirred for 15 hr. at room temperature and the solvent was removed in vacuo to give 1-[(2,6-Dichlorophenyl)methyl]-L-histidine methyl ester, dihydrochloride salt.

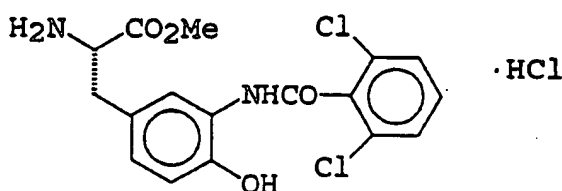
R. Example 7. 3-Nitro-L-tyrosine methyl ester, hydrochloride salt.



To a solution of N-(tert-butoxycarbonyl)-L-tyrosine methyl ester (5.64 g) in THF (10 ml) was added NH_4NO_3 (3 g) and concentrated HNO_3 (3 ml). After 30 sec., the reaction mixture turned to dark red with reflux occurring. The reaction mixture was quenched with solid NaHCO_3 and H_2O , and extracted with AcOEt. The extract was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent; Hexane → 1:1, Hexane/AcOEt) to give N-(tert-butoxycarbonyl)-3-nitro-

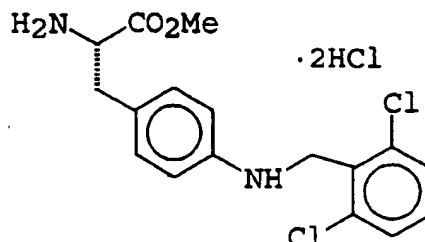
L-tyrosine methyl ester (3.42 g). The obtained compound was treated in a similar manner as described in R. Example 4 to give 3-Nitro-L-tyrosine methyl ester, hydrochloride salt.

- 5 R. Example 8. 3-[(2,6-Dichlorobenzoyl)amino]-L-tyrosine methyl ester, hydrochloride salt.



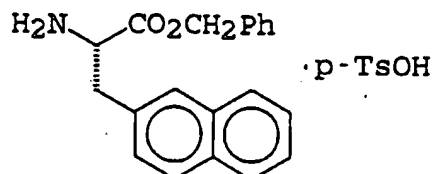
- A mixture of N-(tert-butoxycarbonyl)-3-nitro-L-tyrosine methyl ester (2.0 g) and 10% Pd-C (1.0 g) in MeOH (10 ml) was subjected to catalytic hydrogenolysis at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was triturated with ether to give 3-amino-N-(tert-butoxycarbonyl)-L-tyrosine methyl ester (1.5 g) as a solid. To a solution of the obtained compound (1.0 g) in CH₂Cl₂ (10 ml) was added 2,6-dichlorobenzoyl chloride (0.74 g) and DIEA (1.1 g) and the mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (eluent; 2:1, Hexane/AcOEt) to give N-(tert-butoxycarbonyl)-3-(2,6-dichlorobenzamido)-L-tyrosine methyl ester (1.2 g). The obtained compound was treated in a similar manner as described in R. Example 4 to give 3-[(2,6-dichlorobenzoyl)amino]-L-tyrosine methyl ester, hydrochloride salt.

R. Example 9. 4-[[(2,6-Dichlorophenyl)methyl]amino]-
L-phenylalanine methyl ester,
hydrochloride salt.



- To a mixture of 4-amino-N-(tert-butoxycarbonyl)-
5 L-phenylalanine methyl ester (0.59 g) and 2,6-
dichlorobenzaldehyde (0.35 g) in MeOH (9 ml) was added
NaCNBH₃ (0.38 g), AcOH (1 ml), and molecular sieves 4A
(catalytic amount) and the mixture was stirred
overnight at room temperature.
- 10 The reaction mixture was quenched with brine and
1N HCl. The solvent was removed in vacuo and the
residue was extracted with AcOEt. The extract was
washed with 1N HCl, brine, dried over MgSO₄, and the
solvent was removed in vacuo. The residue was
15 purified by column chromatography on silica gel
(eluent; 10% EtOH/CH₂Cl₂) to give N-(tert-
butoxycarbonyl)-4-[[(2,6-dichlorophenyl)methyl]amino]-
L-phenylalanine (0.36 g) as a colorless solid. The
obtained compound (0.5 g) was dissolved in MeOH (5 ml)
20 and HCl gas was bubbled for 5 min. at 0°C. The
mixture was stirred for 2 hr. and the solvent was
removed in vacuo to give 4-[[(2,6-
Dichlorophenyl)methyl]amino]-L-phenylalanine methyl
ester, hydrochloride salt.

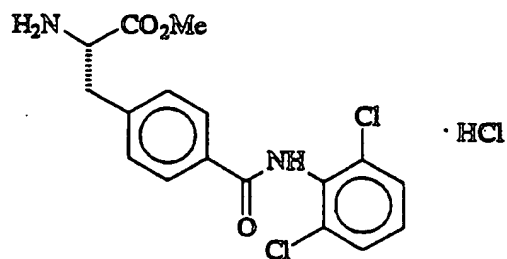
R. Example 10. (S)- α -Amino-2-naphthalenepropanoic acid phenylmethyl ester, 4-methylphenylsulfonic acid salt.



A mixture of (S)-2-amino-3-(2-naphthyl)-propanoic acid (0.40 g), benzyl alcohol (2 ml), and p-toluenesulfonic acid monohydrate (0.42 g) in toluene (5 ml) was heated for 6 hr. under reflux.

The reaction mixture was cooled and diluted with ether (10 ml)/hexane (10 ml). The resulting precipitate was collected by filtration and recrystallized from EtOH/ether to give (S)- α -Amino-2-naphthalenepropanoic acid phenylmethyl ester, 4-methylphenylsulfonic acid salt (0.73 g), mp 174-176°C.

R. Example 11. 4-[[[(2,6-Dichlorophenyl)amino]carbonyl]-L-phenylalanine methyl ester, hydrochloride salt.

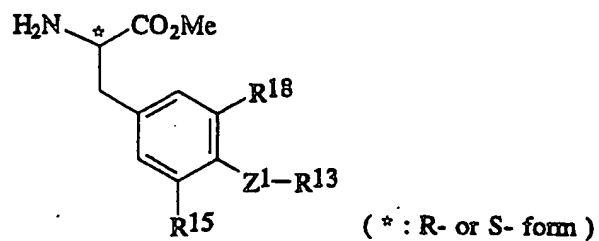


A solution of 4-bromo-N-(tert-butoxycarbonyl)-L-phenylalanine (359 mg) in THF was added to a THF solution of n-BuLi (2.7 ml of 1.6 M solution in hexane) at -78°C. The mixture was stirred for 2 hr.

- at room temperature, quenched with 1N HCl (15 ml), and extracted with AcOEt. The extract was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on
- 5 silica gel (eluent: Hexane \rightarrow AcOEt) to give N-(tert-butoxycarbonyl)-4-[(2,6-dichlorophenyl)-carbamoyl]-L-phenylalanine (95 mg). The obtained compound was treated in a similar manner as described in R. Example 4 to give 4-[(2,6-Dichlorophenyl)amino]carbonyl]-L-
- 10 phenylalanine methyl ester, hydrochloride salt.

R. Examples 12-46 were prepared in a similar manner as described in R. Examples 4-11, and are shown in the Tables 6-8.

Table 6.

R. Examples 12 through 26:

R.Ex. No.	*	R ¹⁵	Z ¹	R ¹³	R ¹⁸
12	S	H	single bond	t-BuO-	H
13	S	H	-OCH ₂ -		H
14	S	H	-OCH ₂ -		H
15	S	H	-OCH ₂ -		H

Table 6 (continued)

298

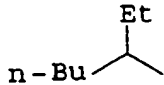
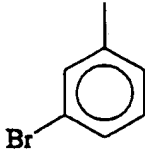
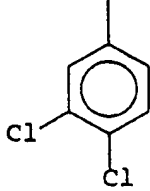
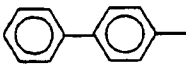
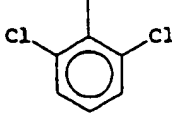
16	S	H	-OCH ₂ -		H
17	S	I	-OCH ₂ -		I
18	S	H	-OCH ₂ -		H
19	S	PhCH ₂ O	-OCH ₂ -	Ph	H
20	S	H	-OCH ₂ -		H
21	S	H	-OCH ₂ -	Ph	H
22	R	H	-OCH ₂ -	Ph	H
23	S	NO ₂	-OCH ₂ -		H

Table 6 (continued) 299

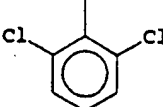
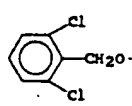
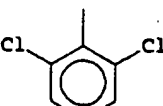
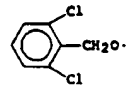
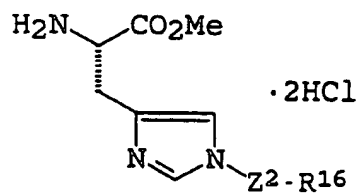
24	S	OH	-OCH ₂ -		H
25	S		-OCH ₂ -		H
26	S		single Bond	OH	H

Table 7

R. Examples 27 through 35:



R.Ex. No.	Z ²	R ¹⁶
27	single bond	Ph ₃ C-

Table 7 (continued)

300

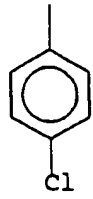
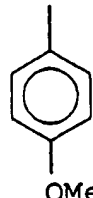
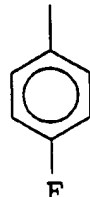
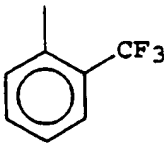
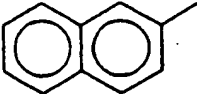
28	CH ₂	
29	CH ₂	Ph
30	CH ₂	
31	CH ₂	PhCH ₂ O
32	CH ₂	
33	CH ₂	
34	CH ₂	

Table 7 (continued)

301

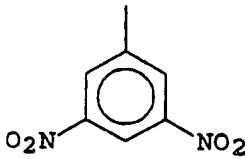
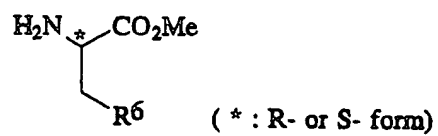
35	CH ₂	
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Table 8

R. Examples 36 through 46:

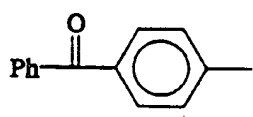
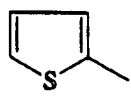
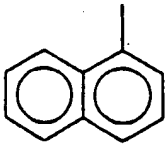
R. Ex. No.	*	R ⁶
36	S	
37	S	
38	S	

Table 8 (continued)

302

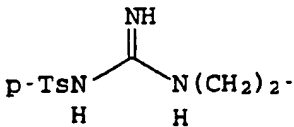
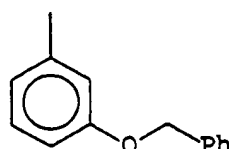
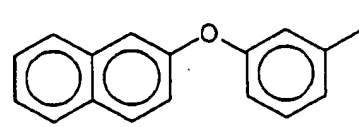
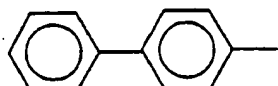
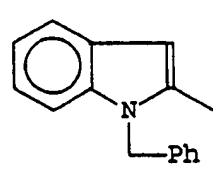
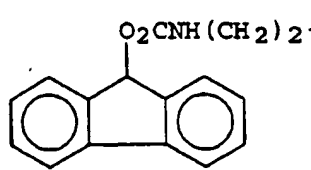
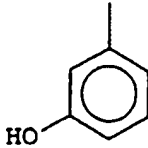
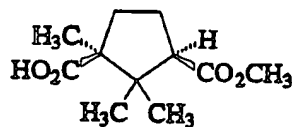
39	S	
40	S	Ph
41	S	
42	S	
43	S	
44	S	
45	S	

Table 8 (continued)

303

46	R	
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R. Example 47. (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 3-methyl ester ($C_{11}H_{18}O_4$), 36-B



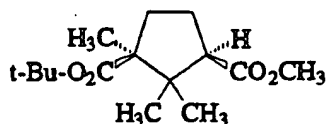
Reference Example 47 was prepared according to Scheme 36: 36-B where R^{36-1} is CH_3 , and the stereochemistry is (1S-cis) as follows:

The preparation follows that of Preparation 10-A using (1S, 3R)-(-)-Camphoric acid as the starting material.

Physical properties as follows: 1H NMR ($CDCl_3$) δ 11.45

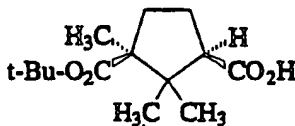
(1 H), 3.69 (3 H), 2.82 (1 H), 2.54 (1 H), 2.24 (1 H), 1.82 (1 H), 1.52 (1 H), 1.27 (3 H), 1.25 (3 H), 0.86 (3 H); Anal: Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47; Found: C, 61.60; H, 8.30.

R. Example 48. (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-3-methyl diester ($C_{15}H_{26}O_4$), 36-C



- 5 Reference Example 48 was prepared according to Scheme 36: 36-C where R^{36-1} is CH_3 , R^{36-2} is t-Bu, and the stereochemistry is (1S-cis) as follows:
To a solution of (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 3-methyl
10 ester (9.69 g), 36-B, in 3 mL of CH_2Cl_2 and 80 mL of cyclohexane was added t-Butyl-2, 2, 2-trichloroacetimidate (16.18 mL) and 35 μ L of $BF_3 \cdot OEt_2 \cdot O$.
The reaction was stirred at ambient temperature for 18 hours and then filtered. The filtrate was purified by
15 flash chromatography silica gel eluting with AcOEt-hexane to obtain (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-3-methyl diester (12.89 g), 36-C.
Physical properties as follows: m.p. = 35-37°C; 1H NMR (CDCl₃) δ 3.68 (3 H), 2.79 (1 H), 2.53 (1 H), 2.17 (1 H), 1.76 (1 H), 1.24 (3 H), 1.17 (3 H), 0.81 (3 H);
20 Anal: Calcd. for $C_{15}H_{26}O_4$: C, 66.64; H, 9.67; Found: C, 66.61; H, 9.64.

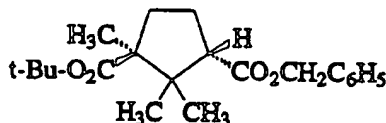
25 R. Example 49. (1S-cis)-1, 2, 2-Trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl) ester ($C_{14}H_{24}O_4$), 36-D



Reference Example 49 was prepared according to Scheme 36 in the Preparation of 36-D where R^{36-2} is t-Bu and the stereochemistry is (1S-cis) as follows:

The preparation follows that of Preparation 15-D using 36-C, (1S-cis)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl)-3-methyl diester, as starting material. Physical properties as follows: m.p. = 95.7-97.5°C; ^1H NMR (CDCl_3) δ 2.82 (1 H), 2.53 (1 H), 2.13 (1 H), 1.82 (1 H), 1.45 (10 H), 1.29 (3 H), 1.17 (3 H), 0.88 (3 H); Anal: Calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_4$: C, 65.60; H, 9.44; Found: C, 65.60; H, 9.44.

R. Example 50. (1S-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester ($\text{C}_{21}\text{H}_{30}\text{O}_4$), 36-E-1



Reference Example 50 was prepared according to Scheme 36: Preparation of 36-E-1 where R^{36-1} is $-\text{CH}_2\text{C}_6\text{H}_5$, R^{36-2} is t-Bu, and the stereochemistry is (1S-trans) as follows:

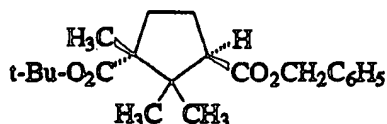
To a solution of (1S-cis)-1, 2, 2-Trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl) ester 36-D (20.0 g) in 300 mL of CH_3CN was added benzyl bromide (16.01 g) and DIEA (12.1 g). The reaction was stirred at ambient temperature for 22 hours, concentrated in vacuo, and diluted with CH_2Cl_2 . The solution was consecutively washed with water, 10 % HCl, water, and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The concentrate was purified by chromatography on silica

gel eluting with AcOEt-hexane to obtain (1S-cis)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester (18.94 g)

- 5 Physical properties as follows: ¹H NMR (CDCl₃) δ 7.34 (5 H), 5.12 (2 H), 2.82 (1 H), 2.51 (1 H), 2.19 (1 H), 1.82 (1 H), 1.44 (10 H), 1.23 (3 H), 1.15 (3 H), 0.78 (3 H); MS (EI) m/z (rel. intensity) 0 (M⁺, 0), 181 (64), 180 (64), 179 (17), 166 (22),
10 155 (16), 153 (15), 109 (18), 92 (15), 91 (99), 57 (40); Anal. Calcd for C₂₁H₃₀O₄: C, 72.80; H, 8.73; Found: C, 70.76; H, 8.38; N, 0.36.

- The product of the above reaction was combined with THF(44 mL) and NaH(634 mg) and refluxed for 0.5 hour
15 then cooled, diluted with saturated NaHCO₃, and extracted with AcOEt. The organic layer was concentrated to obtain a mixture of starting material and (1S-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester. These were separated by HPLC on
20 an (R, R)Whelk-O, 5 x 25 cm column, eluting with 2% isopropanol in hexane at 50 mL/minute. The detector monitored 215 nm. The first peak at 19 minutes contained (1S-trans)-[1-(Phenylmethoxy)carbonyl]-1, 2,
25 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester 36-E-1(3.88 g). Physical properties as follows: ¹H NMR (CDCl₃) δ 7.34 (5 H), 5.12 (2 H), 3.02 (1 H), 2.18 (2 H), 1.98 (1 H), 1.58 (1 H), 1.44 (9 H), 1.08 (3 H), 1.06 (3 H), 0.79 (3 H);
30 MS (FAB) m/z 347 (MH⁺), 501, 292, 291, 245, 183, 109, 92, 91, 57, 41; HPLC 0.46x25 cm (R, R)Whelk-O column eluted at 0.5 mL/minute with 2% isopropanol in hexane, monitoring 215 nm, RT = 13.65 minutes.

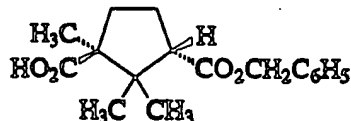
R. Example 51. (1R-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester (C₂₁H₃₀O₄), 36-E-2



5 Reference Example 51 was prepared according to Scheme 36: Preparation of 36-E-2 where R³⁶⁻¹ is -CH₂C₆H₅, R³⁶⁻² is t-Bu, and the stereochemistry is (1R-trans) as follows:

10 The preparation follows that of Preparation 36-E-1 using 15-D, (1R-cis)-1, 2, 2-Trimethylcyclopentane-1,3-dicarboxylic acid 1-(1, 1-dimethylethyl) ester, as starting material. Physical properties as follows: ¹H NMR (CDCl₃) δ 7.35 (5 H), 5.12 (2 H), 3.02 (1 H), 2.13 (2 H), 1.98 (1 H), 1.58 (1 H), 1.44 (9 H), 1.08 (3 H),
15 1.05 (3 H), 0.78 (3 H); HPLC 0.46x25 cm (R, R)Whelk-O column eluted at 1.0 mL/minute with 2% isopropanol in hexane, monitoring 254 nm, RT = 5.54 minutes

R. Example 52. (1S-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid (C₁₇H₂₂O₄), 36-F-1



Reference Example 52 was prepared according to Scheme 36: Preparation of 36-F-1 where R³⁶⁻¹ is -CH₂C₆H₅, and the stereochemistry is (1S-trans) as follows:

A sample of 36-E-1, (1S-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester (2.95 g), was dissolved in TFA at

0°C and then allowed to come to ambient temperature.

The solution was stirred for 19 hours then

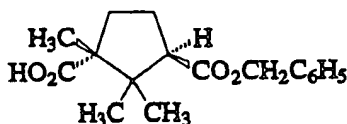
concentrated, redissolved in t-butyl methyl ether and washed with a saturated solution of NaHCO₃. The

5 organic layer was concentrated in vacuo to obtain (1S-trans)-[3-(phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 36-F-1 (2.44 g).

Physical properties as follows: ¹H NMR (CDCl₃) δ 7.34

10 (, 5 H), 5.13 (, 2 H), 3.08 (, 1 H), 2.16 (, 2 H), 2.02 (, 1 H), 1.64 (, 1 H), 1.16 (, 3 H), 1.10 (, 3 H), 0.83 (, 3 H); Anal. Calcd for C₁₇H₂₂O₄: C, 70.32; H, 7.64. Found: C, 70.94; H, 7.63; N, 0.04.

15 R. Example 53. (1R-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid (C₁₇H₂₂O₄), 36-F-2



Reference Example 53 was prepared according to Scheme 36: Preparation of 36-F-2 where R³⁶⁻¹ is -CH₂C₆H₅, and the stereochemistry is (1R-trans) as follows:

20 The preparation follows that of Preparation 36-F-1 using 36-E-2, (1R-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester, as starting material. Physical properties as follows:

25 MS (EI) m/z (rel. intensity) 290 (M⁺, 5), 183 (15), 182 (9), 164 (8), 153 (22), 136 (10), 109 (22), 92 (24), 91 (99), 65 (9), 55 (9); Anal. Calcd for C₁₇H₂₂O₄: C, 70.32; H, 7.64. Found: C, 70.66; H, 7.74; N, 0.22.

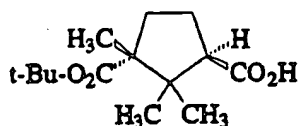
R. Example 54. (1S-trans)-1, 2, 2-trimethylcyclopentane-1, 3-dicarboxylic acid 1-(1, 1-dimethylethyl) ester ($C_{14}H_{24}O_4$), 36-G-1



- 5 Reference Example 54 was prepared according to Scheme 36: Preparation of 36-G-1 where R^{36-2} is t-Bu and the stereochemistry is (1S-trans) as follows:
A sample of 36-E-1, (1S-trans)-[3-(Phenylmethoxy)carbonyl]-1, 2, 2-
- 10 trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester (3.27 g), was dissolved in EtOH (100 mL) and added 5% palladium on carbon (1.0 g) and cyclohexene (50 mL). The mixture was refluxed for 4 hours and then stirred at ambient temperature for 18
- 15 hours. The reaction was then filtered and the filtrate concentrated in vacuo to obtain 36-G-1, (1S-trans)-1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester (2.45 g). Physical properties as follows: 1H NMR ($CDCl_3$) δ 3.05 (1 H),
- 20 2.11 (2 H), 1.99 (1 H), 1.60 (1 H), 1.45 (9 H), 1.11 (3 H), 1.10 (3 H), 0.89 (3 H); MS (FAB) m/z (rel. intensity) 257 (MH^+ , 43), 411 (23), 257 (43), 201 (99), 183 (20), 177 (14), 155 (26), 109 (36), 57 (81), 41 (22), 29 (15);
- 25 Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.62; H, 9.42; N, 0.03.

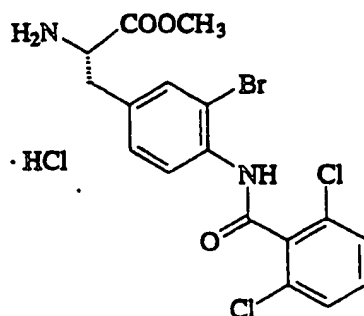
310

R. Example 55. (1R-trans)-1, 2, 2-trimethylcyclopentane-1,3-dicarboxylic acid 1-(1, 1-dimethylethyl) ester ($C_{14}H_{24}O_4$), 36-G-2



- 5 Reference Example 55 was prepared according to Scheme 36: Preparation of 36-G-2 where R^{362} is t-Bu and the stereochemistry is (1R-trans) as follows:
The preparation follows that of Preparation 36-G-1 using 36-E-2, (1R-trans)-[3-(Phenylmethoxy)carbonyl]-
10 1, 2, 2-trimethylcyclopentane-1-carboxylic acid 1-(1, 1-dimethylethyl) ester, as starting material. Physical properties as follows: 1H NMR ($CDCl_3$) δ 3.03 (, 1 H), 2.13 (, 2 H), 1.98 (, 1 H), 1.59 (, 1 H), 1.45 (, 9 H), 1.11 (, 3 H), 1.10 (, 3 H), 0.89 (, 3 H); MS
15 (FAB) m/z (rel. intensity) 257 (MH^+ , 35), 411 (19), 279 (14), 257 (35), 201 (99), 183 (18), 155 (26), 109 (35), 57 (74), 41 (19), 29 (12); Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.56; H, 9.44; N, 0.18.

- 20 R. Example 56. 3-Bromo-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester hydrochloride salt ($C_{17}H_{15}BrCl_2N_2O_3 \cdot HCl$).

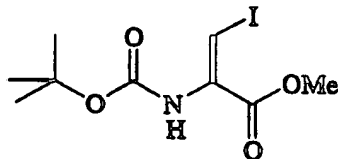


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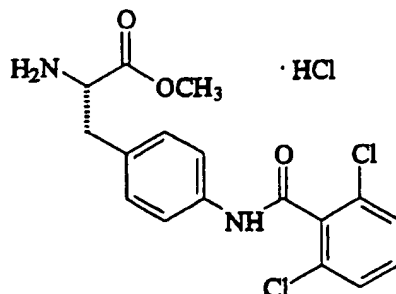
Reference Example 56 was prepared as follows:

To a solution of 4-[(2, 6-Dichlorobenzoyl)amino]-L-phenylalanine methyl ester hydrochloride salt, 37-B-1, (205.7 mg) in acetic acid (5 mL) was added an excess
5 of bromine (5.55 g) in acetic acid (5 mL) and iron powder (416.2 mg). The reaction was stirred at ambient temperature for 3 hours. The reaction concentrated in vacuo and the remaining acetic acid removed as an azeotrope with toluene. The crude material was
10 diluted with water, made basic with saturated sodium bicarbonate and extracted with AcOEt. The extract was purified by flash chromatography on silica gel eluting with methanol-methylene chloride. The purified material was dissolved in methanol saturated with
15 hydrogen chloride and concentrated in vacuo and then crystallized from methanol with AcOEt to obtain 3-Bromo-4-[(2, 6-dichlorobenzoyl)amino]-L-phenylalanine methyl ester hydrochloride salt (540.4 mg). Physical properties as follows: m.p. 200-205; ¹H NMR (CD₃OD) δ
20 7.76 (1 H), 7.64 (1 H), 7.46 (3 H), 7.34 (1 H), 4.38 (1 H), 3.85 (3 H), 3.30 (1 H), 3.15 (1 H); HRMS (FAB) Calcd for C₁₇H₁₅BrCl₂N₂O₃·H₁ 444.9722, found 444.9724.

R. Example 57. N-[(1,1-Dimethylethoxy)carbonyl]-3-iodo-L-alanine methyl ester (C₉H₁₆INO₄).



25 The preparation of Reference Example 57 is taught by Scheme 39 under the heading Preparation of Reference Example 57.

R. Example 58.

The aminoester product of Reference Example 58 is useful as a synthetic intermediate (for example, reagent 37-B of Scheme 37). Reference Example 58 is prepared as follows:

To a cold ($0-5^\circ\text{C}$) solution of anhydrous methanolic HCl was added 100 g of L-4-nitrophenylalanine (Advanced ChemTech) portionwise over 15 min. The mechanically stirred mixture was heated to gentle reflux for 48 h. The mixture was allowed to cool and then filtered through a sintered glass filter funnel, washing the collected solids with hot MeOH until only insoluble residues remained. The filtrate was concentrated in vacuo to afford the methyl ester (120 g) as waxy off white solid which was used without further purification.

To a suspension of methyl ester described above (87 g, 0.33 mole) in CH_2Cl_2 (1500 mL) at ambient temperature was added di-*t*-butyldicarbonate (109 g, 0.50 mole) followed by the dropwise addition of Et_3N (51 mL, 0.37 mole). After 15 min additional Et_3N (40 mL, 0.29 mol) was added to maintain a slightly basic mixture (ca. pH 8). The reaction mixture was stirred 18 h and additional CH_2Cl_2 (1400 mL) and Et_3N (15 mL, 0.11 mol) were added. After an additional 2 h the reaction mixture was quenched by the slow addition of MeOH (100 mL), stirred for 1 h and then partitioned between CH_2Cl_2 and cold 10% aqueous KHSO_4 . The organic layer was washed with saturated NaHCO_3 and brine, dried

(Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography of the residue using hexane and a gradient of a 1:1 mixture of $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ (25-33%) afforded the Boc-methyl ester (69 g) as a white solid. Physical properties as follows: ^1H NMR (300 MHz; CDCl_3) δ 8.16 (2H), 7.31 (2H), 5.04 (1H), 4.63 (1H), 3.73 (3H), 3.18 (2H), 1.41 (9H); MS (ES+) for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_6$ m/z 325.2 ($\text{M}+\text{H}$) $^+$.

Palladium on carbon (10% w/w, 1.25 g) was added to a Parr hydrogenation flask under a N_2 atmosphere and carefully wetted with 100 mL of MeOH/THF (1:1). A solution of the Boc-methyl ester described above (25 g, 77 mmol) in 400 mL of MeOH/THF (1:1) was added and the mixture shaken on a hydrogenation apparatus under a hydrogen atmosphere (20 psi) for 1 h at ambient temperature. The reaction mixture was filtered through a pad of Celite and the solids washed several times with MeOH . The combined filtrates were concentrated in vacuo to afford the 4-aminophenylalanyl derivative (22.7 g) which was used without further purification. Physical properties as follows: ^1H NMR (300 MHz, CDCl_3) δ 6.89 (2H), 6.61 (2H), 4.96 (1H), 4.50 (1H), 3.69 (3H), 2.95 (2H), 1.41 (9H); MS (ES+) for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_4$ m/z 295.2 ($\text{M}+\text{H}$) $^+$.

A cold (0-5°C) solution of 2,6-dichlorobenzoyl chloride (11.1 mL, 77.5 mmol) in 125 mL of THF was treated dropwise with a solution of the 4-aminophenylalanyl derivative described above (22.7 g, 77.1 mmol) and Et_3N (16 mL, 115 mmol) in 125 mL of THF. The reaction mixture was allowed to warm to temperature and stir an additional 18 h. The mixture was diluted with EtOAc (2 L) and then washed with 1N HCl , H_2O , 1N NaOH and brine. The organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product as a pale yellow solid. This material was recrystallized from acetone/hexanes (ca. 1:1) to afford the amide (30.8 g) as a crystalline solid. Physical properties as follows: mp 192.2-

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193.1°C; IR (mull) 3305, 1747, 1736, 1690, 1665, 1609, 1548, 1512, 1433, 1414, 1325, 1277, 1219, 1171, 781 cm⁻¹; ¹H NMR (300 MHz; CDCl₃) δ 7.57 (2H), 7.34 (4H), 7.14 (2H), 4.98 (1H), 4.60 (1H), 3.74 (3H), 3.11 (2H), 1.42 (9H); MS (ES+) for C₂₂H₂₄Cl₂N₂O₅ m/z 467.0 (M+H)⁺.

To 650 mL of anhydrous 4M HCl in dioxane at ambient temperature was added the amide described above (30.6 g, 65.5 mmol) portionwise and the resulting mixture was stirred until all the solids had dissolved (ca. 1 h). Volatiles were removed in vacuo to give a light yellow solid which was partitioned between water (500 mL) and ether (1 L). The water layer was separated and concentrated in vacuo to approximately 200 mL. The aqueous solution was then frozen and lyophilized to afford the aminoester product Reference Example 58 (25.6 g) as a light yellow solid. Physical properties as follows: [α]_D²⁵ = +5 (c 1, MeOH); IR (mull) 3244, 3186, 3112, 1747, 1660, 1604, 1562, 1539, 1516, 1431, 1416, 1327, 1273, 1243, 799 cm⁻¹; ¹H NMR (300 MHz; CD₃OD) δ 7.69 (2H), 7.45 (3H), 7.29 (2H), 4.34 (1H), 3.83 (3H), 3.21 (2H); ¹³C NMR (300 MHz; CD₃OD) δ 169.0, 163.9, 137.8, 136.08, 131.8, 131.0, 130.3, 129.7, 127.9, 120.6, 53.8, 52.3, 35.4; MS (ES+) for C₁₇H₁₆Cl₂N₂O₅ m/z 367.1 (M+H)⁺.

25 Biological Assays

Jurkat-Endothelial Cell Adhesion Assay:

The following assay established the activity of the present compounds in inhibiting β₁-mediated cell adhesion in a representative in vitro system. This assay measures the adhesive interactions of a T-cell line, Jurkat, known to express the α₄β₁ integrin, to endothelial monolayers in the presence of test compounds. The test compounds were added in increasing concentrations to T-cells and then the T-cell compound mixture was added to IL-1 stimulated endothelial cell monolayers. The plates were incubated, washed and the percentage of attached cells

was quantitated. The present assay directly demonstrates the cell adhesion inhibitory activity and adhesion modulatory activity of the compounds.

Human umbilical vein endothelial cells were purchased from Clonetics (San Diego, CA.) at passage number 2. The cells were grown on 0.5% porcine skin gelatin pre-coated flasks (Sigma, St. Louis MO.) in EGM-UV media (Clonetics, San Diego, CA) supplemented with 10% fetal bovine serum. Cells are refed every 2-3 days reaching confluence by day 4 to 6. The cells are monitored for factor VIII antigen and results show that at passage 12, the cells are positive for this antigen. The endothelial cells are not used following passage 6.

The T-cell line Jurkat was obtained from American Type Tissue Culture Collection (Rockville, MD) and the cells were cultured in RPMI containing 10 % fetal calf serum. The cells were washed twice in Hank's Balanced Salt Solution (HBSS) and resuspended in Dulbecco's Minimal Eagle's Media (DMEM) containing 2.5 mg/ml Human Serum Albumin (HSA). Jurkat cells (1×10^6 cells/ml) were stained with 10 ng/ml BCECF-AM (Molecular Probes, Eugene, OR) in HBSS without phenol red. The cells were loaded with BCECF for 60 minutes in the dark at 37°C, washed 2 times, and resuspended in DMEM-HSA solution.

Confluent endothelial monolayers, grown in 96-well tissue culture plates, were stimulated for 4 hr. at 37 °C with 0.1 ng/ml (~50 U/ml) recombinant IL-1 (Amgen, Thousand Oaks, CA). Following this incubation, the monolayers were washed twice with HBSS and 0.1 ml of DMEM-HSA solution was added. Jurkat cells (5×10^5 cells) were combined with the appropriate concentration of the test compound and 0.1 ml of the Jurkat cell-compound mixture was added to the endothelial cell monolayers. Generally, 100, 20, 5 and 1.25 μ M compound concentrations were tested. These concentrations are adjusted downward for analogs found or thought to be more potent. The plates were placed on ice for 5 minutes to allow for Jurkat cell

settling and the plates were incubated at 37 °C for 20 minutes. Following this incubation, the monolayers were washed twice with PBS containing 1 mM calcium chloride and 1 mM magnesium chloride and the plates were read using a Millipore Cytofluor 2300 (Marlboro, MA.). Fluorescence in each well was measured as Arbitrary Fluorescence Units and percent adhesion in the absence of compound was adjusted to 100% and the % adhesion in the presence of compound was calculated. Monolayers were also fixed in 3% paraformaldehyde and evaluated microscopically to verify the adhesion. This procedure is a modification of a previously published method (Cardarelli et al., *J. Biol. Chem.* 269:18668-18673 (1994)).

Jurkat-CS-1 assay

The CS-1 derived peptide, CLHPGEILDVPST, and the scrambled control peptide, CLHGPIELVSDPT, were synthesized on a Beckman 990 synthesizer using t-Boc methodology. The peptides were immobilized onto microtiter plates using the heterobifunctional crosslinker 3-(2-pyridyldithio)propionic acid N-hydroxysuccinimide ester (SPDP) as reported by Pierschbacher et al., *Proc. Natl. Acad. USA*, 80:1224-1227 (1983). Microtiter plates were coated with 20 µg/ml HSA for 2 hr. at room temperature, washed once with PBS and derivatized with 10 µg/ml SPDP for 1 hr. After washing, 100 µl of a 100 µg/ml cysteine containing peptide solution which had been recently dissolved was added to the wells and allowed to crosslink to the plates overnight at 4 °C. Unbound peptide was removed from plates by washing with PBS. To block non-reacted sites, the plates are coated with 100 µl of a 2.5 mg/ml BSA solution in PBS for 1 hr. at 37 °C. 100 µl of Jurkat cells (2.5 x 10⁶ cells/ml) in DMEM plus BSA (2.5 mg/ml) was mixed with an appropriate concentration of the compound to be tested and the mixture was added to peptide coated dishes and incubated for 1 hr. at 37 °C. Generally 100, 20, 5 and

1.25 μM concentrations of the compound were tested. The concentrations of the compound were adjusted downward for compounds thought or found to be more potent.

5 Following this incubation the plates were washed once with PBS and the attached cells were fixed with 3% paraformaldehyde in PBS and stained with 0.5% toluidine blue in 3.7% formaldehyde. The cells were stained overnight at room temperature and the optical
10 density at 590 nm of toluidine blue stained cells was determined using a vertical pathway spectrophotometer to quantitate attachment (VMAX Kinetic Microplate Reader, Molecular Devices, Menlo Park, CA). This procedure is a modification of a previously published
15 method (Cardarelli et al, J. Biol. Chem., 269:18668-18673 (1994) and Cardarelli et al, Proc. Natl. Acad. Sci. USA, 83:2647-2651 (1986)).

 The preferred compounds are those which have low IC_{50} values in the Jurkat EC assay or the Jurkat-CS-1
20 assay described above or which have at least moderate activity in both assays. All of the compounds of the present invention have an activity of less than 50 μM in the Jurkat CS-1 assay or less than 500 μM in the Jurkat EC assay. Compounds with activity in the
25 Jurkat CS-1 assay preferably have IC_{50} values of less than 1 μM , more preferably less than 0.5 μM , most preferably less than or equal to 0.08 μM . Compounds with activity in the Jurkat EC assay preferably have
30 IC_{50} values of less than 10 μM , more preferably less than 5 μM , most preferably less than or equal to 0.8 μM .

 In the Jurkat EC Assay, IC_{50} value ranges (μM) are depicted by A, B, and C and in the Jurkat CS-1 Assay, IC_{50} value ranges are depicted by D, E, and F. These ranges are as follows:

35 Jurkat EC: $5 \leq A < 10$, $0.8 < B < 5$, and $C \leq 0.8$
 Jurkat CS-1: $0.5 \leq D < 1$, $0.08 < E < 0.5$, and $F \leq 0.08$

The following chart illustrates the IC₅₀ values for selected compounds of the present invention in the Jurkat EC Assay and the Jurkat CS-1 Assay. The ranges are as described above.

5

ADDITIONAL IN VITRO BIOLOGICAL DATA

	Example No.	Jurkat EC	Jurkat CS-1
10	2	-	D
	4	B	E
	10	B	E
	12	C	F
	13	A	D
15	14	A	-
	16	A	-
	24	B	E
	26	B	D
	28	B	E
20	29	A	D
	31	A	-
	36	A	D
	38	B	E
	46	B	-
25	53	B	D
	54	C	F
	61	B	E
	62	A	-
	63	B	F
30	65	C	E
	75	B	-
	77	B	E
	79	A	-
	81	C	E
	83	C	F

	Example No.	Jurkat EC	Jurkat CS-1
	85	A	E
	86	-	D
	87	C	F
	89	B	E
5	91	B	F
	92	C	F
	93	C	F
	95	B	E
	96	A	-
10	97	C	F
	100	C	F
	102	C	F
	103	C	F
	104	C	F
15	105	B	E
	106	C	F
	108	C	F
	110	C	F
	112	C	F
20	113	-	D
	114	C	E
	116	C	F
	118	B	D
	120	B	E
25	121	B	D
	122	B	-
	124	B	E
	126	B	E
	128	B	E
30	130	B	E
	132	B	E
	134	B	-

	Example No.	Jurkat EC	Jurkat CS-1
	136	A	D
	137	-	E
	141	B	D
	142	B	E
5	143	-	D
	144	B	E
	146	B	E
	148	C	E
	150	B	D
10	152	C	F
	153	B	E
	155	A	D
	161	B	-
	163	-	D
15	166	C	F
	170	A	-
	179	A	F
	180	C	F
	181	C	F
20	182	C	F
	183	C	F
	184	C	F
	185	B	E
	186	B	E
25	187	B	E
	188	B	E
	189	B	-
	194	B	E
	208	C	E
30	209	C	F
	210	C	F
	211	C	F

Example No.	Jurkat EC	Jurkat CS-1
212	A	E
213	B	E
214	C	F
215	C	E
216	C	F
217	C	F
219	C	F
220	B	E
221	A	D
222	C	E
223	C	F
225	C	F
231	C	D
232	C	F
236	C	E
253	B	E
254	B	E

Activity of Camphoric Acids in Dextran Pleurisy Model

Certain compounds of the present invention were tested in a Dextran® pleurisy model.

Rationale for Developing an $\alpha\beta_1$ Integrin Antagonist to Treat Inflammatory Diseases

VLA-4, a member of the β_1 integrin family of adhesion molecules, is thought to play a critical role in several types of inflammatory disease processes by promoting leukocyte adhesion to vascular cell adhesion molecule (VCAM-1) and the CS-1 domain of fibronectin in extracellular tissue matrix (Ellices MJ, Osborn L, Takada Y, Crouse C, Luhowskyj S, Hemler M, Lobb RR. VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distinct from the

- VLA-4-fibronectin binding site. Cell; 60: 577-584, 1990, Humphries MJ, Akiyama SK, Komoriya A, Olden K, Yamada KM. Identification of an alternatively-spliced site in human plasma fibronectin that mediates cell type-specific adhesion. J Cell Biol; 103: 2637-2647, 1986, Wayner EA, Garcia-Pardo A, Humphries MJ, McDonald JA, Carter WG. Identification and characterization of the T lymphocyte adhesion receptor for an alternative cell attachment domain (CS-1) in plasma fibronectin. J Cell Biol; 109: 1321-1330, 1989, Guan J-L, Hynes RO. Lymphoid cells recognize an alternatively-spliced segment of fibronectin via the integrin $\alpha_4\beta_1$. Cell; 60: 53-61, 1990) Of the cell types expressing VLA-4, the major emphasis has been on eosinophils, lymphocytes, and monocytes. Validation of the role of VLA-4 has relied predominantly on the use of anti-VLA-4 antibodies which have been shown to suppress delayed-type hypersensitivity responses (Issekutz TB. Dual inhibition of VLA-4 and LFA-1 maximally inhibits cutaneous delayed-type hypersensitivity-induced inflammation. Am J Pathol; 143: 1286-1293, 1993, Scheynius A, Camp RL, Puré E. Reduced contact sensitivity reactions in mice treated with monoclonal antibodies to leukocyte function-associated molecule-1 and intercellular adhesion molecule-1. J Immunol; 150: 655-663, 1993, Ferguson TA, Kupper TS. Antigen-independent processes in antigen-specific immunity. J Immunol; 150: 1172-1182, 1993, Chisholm PL, Williams CA, Lobb RR. Monoclonal antibodies to the integrin α_4 subunit inhibit the murine contact hypersensitivity response. Eur J Immunol; 23: 682-688, 1993, Elices MJ, Tamraz S, Tollefson V, Vollger LW. The integrin VLA-4 mediates leukocyte recruitment to skin inflammatory sites in vivo. Clin Exp Rheumatol; 11 (Suppl 8) S77-80, 1993, experimental allergic encephalomyelitis (Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman LM, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha_4\beta_1$ integrin.

- Nature; 356: 63-66, 1992, Canella B, Raine CS. The VCAM-1/VLA-4 pathway is involved in chronic lesion expression in multiple sclerosis (MS). J Neuropathol Exp Neurol; 52: 311, 1993), HIV-induced encephalitis (Sasseville VG, Newman W, Brodie SJ, Hesterberg P, Pauley D, Ringler DJ. Monocyte adhesion to endothelium in simian immunodeficiency virus-induced AIDS encephalitis is mediated by vascular cell adhesion molecule-1/ $\alpha_4\beta_1$ integrin reactions. Am J Pathol; 144: 27-40, 1994), pulmonary inflammation and airway hyperreactivity in asthma (Abraham WM, Sielczak MW, Ahmed A, Cortes A, Lauredo IT, Kim J, Pepinsky B, et al. α -integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep. J Clin Invest; 93: 776-787, 1994, Pretolani M, Ruffié C, Roberto LapaeSilva J, Joseph D, Lobb RR, Vargaftig BB. Antibody to very late activation antigen 4 prevents antigen-induced bronchial hyperreactivity and cellular infiltration in the guinea-pig airways. J Exp Med; 180: 795-805, 1994), experimental models of autoimmune-mediated diabetes (Yang X-D, Karin N, Tisch R, Steinman L, McDevitt HO. Inhibition of insulinitis and prevention of diabetes in non-obese diabetic mice by blocking L-selectin and very late antigen 4 adhesion receptors. Proc Natl Acad Sci USA; 90: 10494-10498, 1993, Burkly LC, Jakubowski A, Hattori M. Protection against adoptive transfer of autoimmune diabetes mediated through very late antigen-4 integrin. Diabetes; 43: 529-534, 1994), and experimental colitis (Podolsky DK, Lobb R, King N, Benjamin CD, Pepinsky B, Sehgal P, et al. Attenuation of colitis in the cotton-top Tamarin by anti- α_4 integrin monoclonal antibody. J Clin Invest; 92: 372-380, 1993). Since eosinophils represent a major component of the inflammatory cell influx in asthmatic lung tissue we developed a simple acute inflammatory model of VLA-4 integrin-dependent eosinophil infiltration which could be used to identify VLA-4 antagonists; such compounds would be of

potential value in the treatment of asthma as well as other diseases in which VLA-4 played a role.

Materials and Methods

Animals, housing and viral testing:

- 5 C57BL/6 mice (Jackson, Bar Harbor, ME;), 6-8 weeks old, weighing 20-25g were used throughout. All mice were acclimated for at least 7-14 days after arrival and maintained under controlled temperature (20-22°C) and a 12 hr daily light cycle (6.00 A.M. - 6.00 P.M.).
- 10 Mice were housed in laminar flow racks and checked biweekly for viral infections (mouse hepatitis virus, minute virus of mice, rodent orphan parvovirus, Sendai) with kits obtained from Oreganon Teknika (Durham, NC) using established enzyme-linked
- 15 immunoabsorbent assays. Mice testing positive for any of the above were omitted from the study. All mice were fed standard laboratory chow (Upjohn Lab Rodent Irradiated Mouse Chow, #5011-3, PMI Feeds, St. Louis, MO) and acidified drinking water (pH 5.0) ad libitum.

20 Induction of Inflammation by Intrapleural Injection of Dextran:

- Intrapleural injections were made using a 27G needle cut to 3-4 mm and blunted by filing. Injections were made by inserting the needle between
- 25 the mid-intercostal ribs on the right side of the thoracic cavity.

- Dextran (MW 5-40x10⁶, St Louis, MO.) was injected as a 10% solution in saline in a volume of
- 30 100µl/mouse. Care was taken to avoid bleeding at the site of injection at which the intercostal muscles were cut to facilitate smooth insertion of the needle.

Quantitation of Pleural Inflammatory Leukocyte

Responses:

- Pleural leukocytes were collected as follows: 4h
- 35 post-induction, pleural inflammatory exudate was removed by washing with 2 x 1.0 ml Ca⁺⁺/Mg⁺⁺ free HBSS

(Gibco, Grand Island, NY) containing 45 mg EDTA/100 ml HBSS, 4°C. Total leukocyte counts were made by hemocytometer following erythrocyte lysis in 2% acetic acid in PBS buffer; exudate leukocyte pellets were resuspended in serum for cytopspin preparations and stained (Diff Quik, Baxter Healthcare, McGraw Park, IL) for differential leukocyte counts (neutrophils, eosinophils, and mononuclear leukocytes). The pleural cavities of mice receiving either no intrapleural injection, or saline were washed and the cells counted in the same way to estimate baseline or saline-induced pleural leukocyte counts respectively.

Administration of drugs:

All drugs were dissolved in PBS and the pH adjusted to 7.5 with NaOH. Each drug was administered intravenously through the retroorbital sinus at hourly intervals (0-3h) starting from time "0" as indicated. Mice were carefully monitored for side effects; none were noted for the series of compounds reported herein.

The following camphoric acid analogues were tested for their inhibitory effects on dextran-induced leukocyte infiltration: Examples 4, 12, 54, 63, 166, 93, 180, 181, 183, 184, 217, Camphoric acid or PBS (saline) was administered iv. as a control. Inhibition of eosinophil infiltration, which was suppressed by anti-alpha-4 Mab (PS/2, 50%), was used as a readout of VLA-4 antagonist activity of the camphoric acids tested. Data for neutrophils are also reported.

Results:

Dextran pleural leukocyte response. The total pleural leukocyte counts were 255×10^4 (± 16 SEM) cells in the normal pleural cavity; of the normal pleural leukocyte population, all cells were mononuclear (a similar response was observed following intrapleural saline injection). Four hours after intrapleural injection

of dextran total pleural leukocyte counts increased to 719×10^4 (± 67 SEM) and comprised 36.8×10^4 (± 4.1 SEM) eosinophils, 292×10^4 (± 25 SEM) neutrophils and 391×10^4 (± 48 SEM) mononuclear leukocytes.

- 5 Inhibition of neutrophils and eosinophil (%Δ) are depicted by A, B and C according to the following ranges: $A \leq -50$, $-50 < B \leq -10$, $-10 < C \leq 0$

Inhibition of dextran pleural leukocyte infiltration by camphoric acids.

10	Treatment Dose (mg/kg) #		%Δ Pleural Leukocytes	
			<u>Neutro</u>	<u>Eos</u>
	Ex. 12	50x4 iv	B	A
		50x2 iv	B	A
	Ex. 54	50x4 iv	B	A
	15 Ex. 4	25x2 iv	-	-
		50x2 iv	B	A
	Ex. 63	25x2 iv	B	B
		50x2 iv	B	B
	Ex. 166	25x2 iv	-	-
	20	50x2 iv	C	B
	Ex. 93	25x2 iv	-	-
		50x2 iv	C	B
	Ex. 181	25x2 iv	B	B
		50x2 iv	B	B
	25 Ex. 180	25x2 iv	B	B
		50x2 iv	B	B
	Ex. 183	25x2 iv	B	B
		50x2 iv	B	B
	Ex. 184	25x2 iv	B	B
	30	50x2 iv	B	A
	Ex. 217	25x2 iv	-	-
		50x2 iv	C	B

Compounds given at 0h, +1h (x2 iv) or 0h, +1h, +2h, +3h

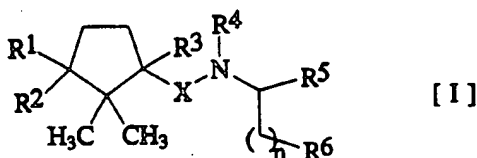
35 (x4 iv) relative to dextran.

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$p < 0.05$ * Drug treated vs camphoric acid or PBS
treated control.

WHAT IS CLAIMED IS:

- 1 1. A compound of the formula [I]:



2 wherein

3 n is an integer of 0 or 1,

4 R¹ is a hydrogen atom or methyl group,

5 R² is a group of the formula: -CN, -COOH,

6 -(C₁₋₆alkylene)OH, -CH₂O(C₁₋₆ alkyl),

7 -(C₁₋₆ alkylene)COOH,

8 -CH₂O(C₁₋₆ alkylene)O(C₁₋₆ alkyl),

9 -CH₂O(C₁₋₆ alkylene)COOH, -(C₂₋₇ alkenylene)COOH,

10 -CO(C₁₋₆ alkylene)COOH, -CO(C₂₋₇ alkenylene)COOH,

11 -CO(C₁₋₆ alkylene)O(C₁₋₆ alkyl),

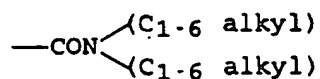
12 -CO(C₁₋₆ alkylene)CO(C₁₋₆ alkyl),

13 -CONH(C₁₋₆ alkyl), -CONHO(C₁₋₆ alkyl),

14 -CONH(C₁₋₆ alkylene)COOH, -CONH₂,

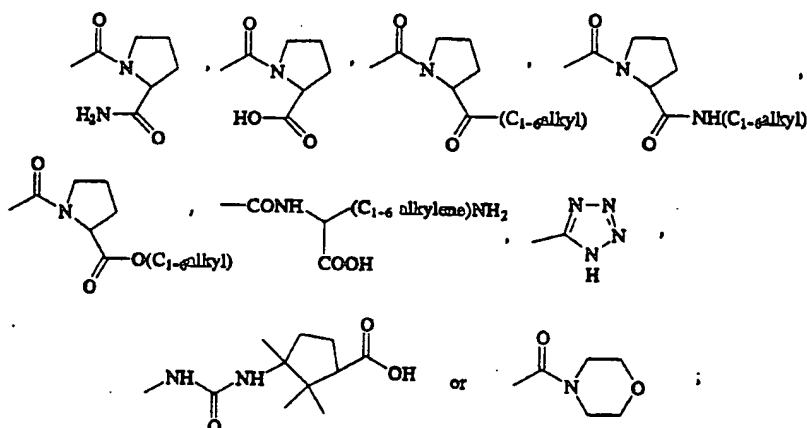
15 -CONH(C₃₋₇ cycloalkyl),

16



329

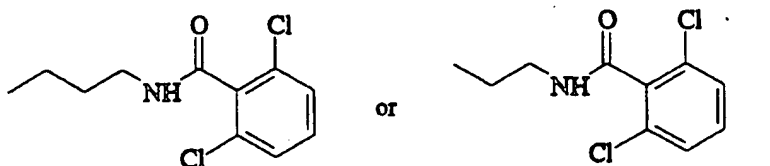
- 17 -CONHOCH₂Ph, -CONH(C₁₋₆ alkylene)CN,
 18 -COO(C₁₋₆ alkyl), -CH₂O(C₁₋₆ alkylene)CONH₂,
 19 -CONH(C₁₋₆ alkylene)CONH₂, -CONHOH,
 20 -NHCOOCH₂Ph,



- 21 R³ is a hydrogen atom or a methyl group,
 22 X is a methylene group or a group of the formula:
 23 -CO-,
 24 R⁴ is a hydrogen atom or a C₁₋₆ alkyl group,
 25 R⁵ is a group of the formula: -COOH or an ester or
 26 an amide thereof, -(C₁₋₆ alkylene)COOH or an ester or an
 27 amide thereof, -(C₁₋₇ alkylene)O(C₁₋₆ alkyl),
 28 -(C₁₋₇ alkylene)OH, -COO(C₁₋₆ alkyl), -CONH(C₁₋₆ alkyl), or
 29 -CONH₂,
 30 R⁶ is a substituted or unsubstituted monocyclic or
 31 bicyclic aryl group, a substituted or unsubstituted
 32 monocyclic or bicyclic heteroaryl group, a substituted
 33 or unsubstituted monocyclic or bicyclic
 34 arylcarbonylamino-C₁₋₆ alkyl group, a substituted or
 35 unsubstituted monocyclic or bicyclic aliphatic
 36 heterocyclic carbonyl group, a
 37 9-fluorenylmethyloxycarbonylamino-C₁₋₆ alkyl group, a

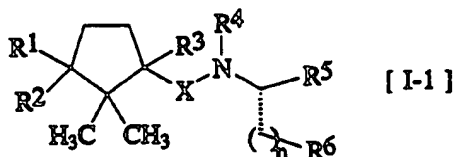
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38 3-tosylguanidino-C₁₋₆ alkyl group,



39 with the proviso that R¹ and R³ must be different and
 40 also with the proviso that when R² or R⁶ is a moiety of
 41 the formula -COOH or contains a moiety of the formula
 42 -COOH, then a pharmaceutically acceptable ester or a
 43 pharmaceutically acceptable amide thereof are
 44 included, and also with the proviso that [1S-
 45 [1 α , (R¹), 3 α]]- α -[[[3-Carboxy-2,2,3-
 46 trimethylcyclopentyl)carbonyl]amino]-4-(2,6-
 47 dichlorobenzoyl)- γ -oxo-1-pyrazinebutanoic acid methyl
 48 ester or [1S-[1 α , (R¹), 3 α]]- β -[[[3-Carboxy-2,2,3-
 49 trimethylcyclopentyl)carbonyl]amino]-4-(2,6-
 50 dichlorobenzoyl)- γ -oxo-1-pyrazinebutanoic acid methyl
 51 ester are excluded; or
 52 a pharmaceutically acceptable salt thereof.

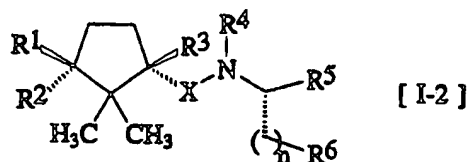
1 2. The compound according to claim 1, which is a
 2 compound of the formula [I-1]:



3 wherein n, R¹ through R⁶ and X are as defined above.

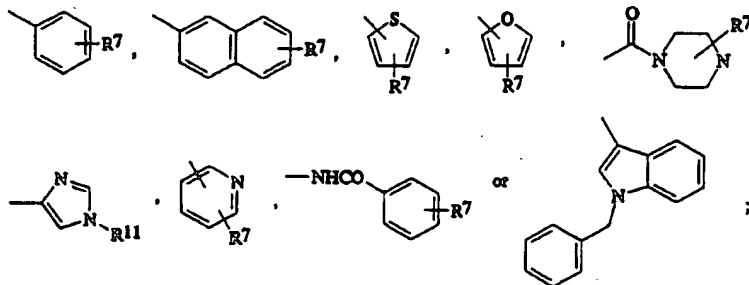
331

- 1 3. The compound according to claim 1 or 2, which
2 is a compound of the formula [I-2]:

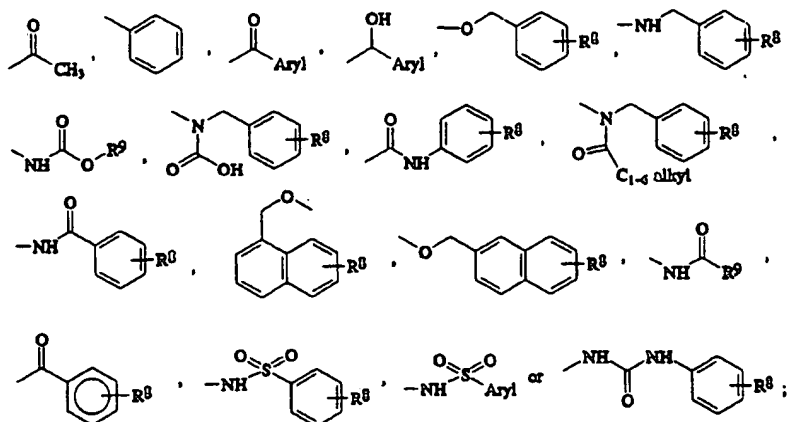


- 3 wherein n, R¹ through R⁴, R⁶ and X are as defined above
4 and R⁵ is a group of the formula: -COOH,
5 -(C₁₋₆ alkylene)COOH, -(C₁₋₇ alkylene)O(C₁₋₆ alkyl),
6 -(C₁₋₇ alkylene)OH, -COO(C₁₋₆ alkyl), -CONH(C₁₋₆ alkyl), or
7 -CONH₂.

- 1 4. The compound according to any one of claims
2 1, 2 and 3, wherein R⁶ is a substituent of the formula:

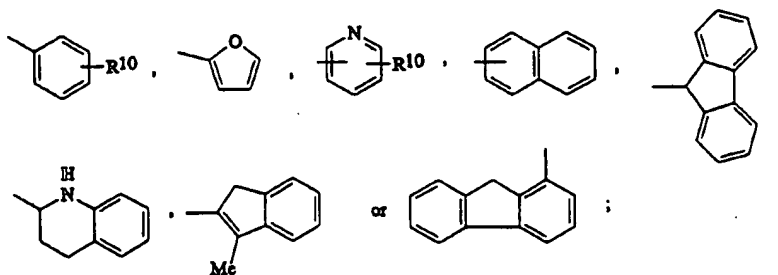


- 3 wherein,
4 R⁷, which occurs one or more times and which may
5 be the same or different in each occurrence, is -H,
6 -OH, -NO₂, -NH₂, -C₁-C₃ alkyl, -F, -Cl, -Br, -I, -COOH,
7 -COO(C₁₋₆ alkyl), -O(C₁₋₈ alkyl),
8 -CONH(C₁₋₆ alkylene)COOH, -OCH₂(C₃-C₇ cycloalkyl) or a
9 substituent of the formula



10 R⁸, which occurs one or more times and which may
 11 be the same or different in each occurrence, is -H,
 12 -OH, -NH₂, -NO₂, -C₁-C₆ alkyl, -F, -Cl, -Br, -I, -CF₃,
 13 phenyl, or -O(C₁₋₆ alkyl);

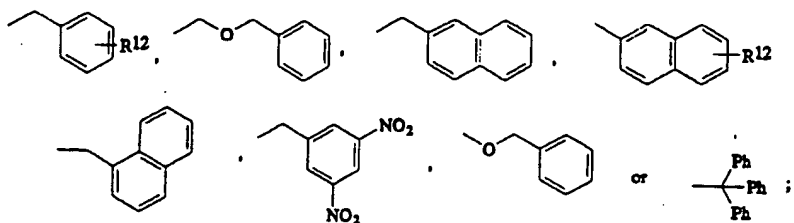
14 R⁹ is selected from a group of the formula: -H,
 15 -C₁-C₆ alkyl, -C₃-C₆ cycloalkyl, -(-C₁-C₆ alkylene)aryl,
 16 aryl, or a substituent of the formula:



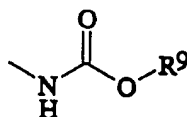
17 R¹⁰, which occurs one or more times and which may
 18 be the same or different in each occurrence, is -H,
 19 -F, -Cl, -Br, -I, -NO₂, -C₁₋₆ alkyl or -O(C₁₋₆ alkyl);

20 R¹¹ is selected from a group of the formula:

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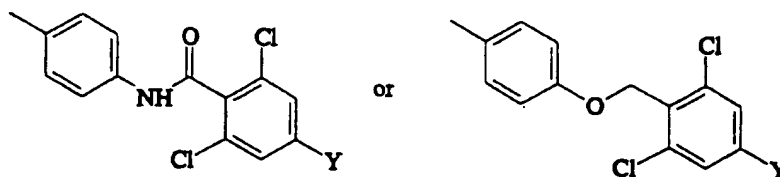


- 21 R^{12} , which occurs one or more times and which may
 22 be the same or different in each occurrence, is -H,
 23 $-CF_3$, $-OCH_3$, -F, -Br, -Cl or -I;
 24 with the proviso that
 25 when R^7 is the formula



- 26 R^9 is other than hydrogen.

- 1 5. The compound according to claim 1, 2, 3 or
 2 4, wherein R^6 is



- 3 wherein
 4 Y is a hydrogen atom or a chlorine atom.

- 1 6. The compound according to claim 1, 2, 3, 4
 2 or 5, wherein R^2 is a group of the formula: $-COOH$ or an
 3 ester or an amide thereof, $-CONHCH_2COOH$, $-CONHOCH_2Ph$ or
 4 $-CONHCH_2CONH_2$.

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1 7. The compound according to claim 1, 2 or 3,
2 wherein

3 R¹ is -CH₃,

4 R² is -COOH, -CONHCH₂COOH, CONHOCH₂Ph or

5 -CONHCH₂CONH₂,

6 R³ is hydrogen,

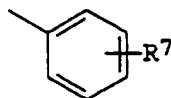
7 X is -CO-,

8 R⁴ is hydrogen,

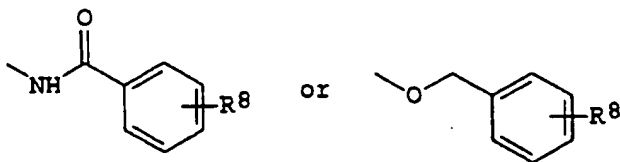
9 R⁵ is -COOH,

10 n is 1, and

11 R⁶ is



12 wherein R⁷ is



13 wherein R⁸ is substituted 2 or 3 times and is -Cl.

1 8. The compound according to claim 1, wherein
2 said compound is selected from the group consisting of
3 Examples 4, 10, 12, 13, 14, 16, 24, 26, 28, 29, 31,
4 36, 38, 46, 53, 54, 61, 62, 63, 65, 75, 77, 79, 81,
5 83, 85, 87, 89, 91, 92, 93, 95, 96, 97, 100, 102, 103,
6 104, 105, 106, 108, 110, 112, 114, 116, 118, 120, 121,
7 122, 124, 126, 128, 130, 132, 134, 136, 141, 142, 144,
8 146, 148, 150, 152, 153, 155, 161, 166, 170, 179, 180,
9 181, 182, 183, 184, 185, 186, 187, 188, 189, 194, 208,
10 209, 210, 211, 212, 213, 214, 215, 216, 217, 219, 220,
11 221, 222, 223, 225, 231, 232 and 236.

1 9. The compound according to claim 8, wherein
2 said compound is selected from the group consisting of
3 Examples 4, 10, 12, 24, 26, 28, 38, 46, 53, 54, 61,
4 63, 65, 75, 77, 81, 83, 87, 89, 91, 92, 93, 95, 97,
5 100, 102, 103, 104, 105, 106, 108, 110, 112, 114, 116,
6 118, 120, 121, 122, 124, 126, 128, 130, 132, 134, 141,
7 142, 144, 146, 148, 150, 152, 153, 161, 166, 180, 181,
8 182, 183, 184, 185, 186, 187, 188, 189, 194, 208, 209,
9 210, 211, 213, 214, 215, 216, 217, 219, 220, 222, 223,
10 225, 231, 232 and 236.

1 10. The compound according to claim 9, wherein
2 said compound is selected from the group consisting of
3 Examples 12, 54, 65, 81, 83, 87, 92, 93, 97, 100, 102,
4 103, 104, 106, 108, 110, 112, 114, 116, 148, 152, 166,
5 180, 181, 182, 183, 184, 208, 209, 210, 211, 214, 215,
6 216, 217, 219, 222, 223, 225, 231, 232 and 236.

1 11. The compound according to claim 1, wherein
2 said compound is selected from the group consisting of
3 Examples 2, 4, 10, 12, 13, 24, 26, 28, 29, 36, 38, 53,
4 54, 61, 63, 65, 75, 77, 81, 83, 85, 86, 87, 89, 91,
5 92, 93, 95, 97, 100, 102, 103, 104, 105, 106, 108,
6 110, 112, 113, 114, 116, 118, 120, 121, 124, 126, 128,
7 130, 132, 136, 137, 141, 142, 143, 144, 146, 148, 150,
8 152, 153, 155, 163, 166, 179, 180, 181, 182, 183, 184,
9 185, 186, 187, 188, 194, 208, 209, 210, 211, 212, 213,
10 214, 215, 216, 217, 219, 220, 221, 222, 223, 225, 231,
11 232 and 236.

1 12. The compound according to claim 11, wherein
2 said compound is selected from the group consisting of
3 Examples 4, 10, 12, 24, 28, 38, 54, 61, 63, 65, 75,
4 77, 81, 83, 85, 87, 89, 91, 92, 93, 95, 97, 100, 102,
5 103, 104, 105, 106, 108, 110, 112, 114, 116, 120, 124,
6 126, 128, 130, 132, 137, 142, 144, 146, 148, 152, 153,

7 166, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188,
8 194, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217,
9 219, 220, 222, 223, 225, 232 and 236.

1 13. The compound according to claim 12, wherein
2 said compound is selected from the group consisting of
3 Examples 12, 54, 63, 83, 87, 91, 92, 93, 97, 100, 102,
4 103, 104, 106, 108, 110, 112, 116, 152, 166, 179, 180,
5 181, 182, 183, 184, 209, 210, 211, 214, 216, 217, 219,
6 223, 225, and 232.

1 14. The compound according to claim 1, wherein
2 said compound is selected from the group consisting of
3 (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-trimethylcyclopentyl)-
4 carbonyl]-1-[(3,4-dichlorophenyl)methyl]-*L*-histidine,
5 (1*S*-*cis*)-*N*-[(3-Carboxy-2,2,3-
6 trimethylcyclopentyl)carbonyl]-*O*-[(2,6-
7 dichlorophenyl)methyl]-*L*-tyrosine, (1*S*-*cis*)-*N*-[(3-
8 Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-
9 dichlorobenzoyl)amino]-*L*-phenylalanine, (1*S*-*cis*)-*N*-
10 [(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-*O*-
11 [(2,6-dichlorophenyl)methyl]-3-nitro-*L*-tyrosine, (1*S*-
12 *cis*)-*N*-[(3-Carboxy-2,2,3-
13 trimethylcyclopentyl)carbonyl]-4-[(2,4,6-
14 trichlorophenyl)carbonyl]-amino]-*L*-phenylalanine, (1*S*-
15 *cis*)-*N*-[[3-[(2-Amino-2-oxoethyl)amino]carbonyl]-
16 2,2,3-trimethylcyclopentyl]carbonyl]-4-[(2,6-
17 dichlorobenzoyl)amino]-*L*-phenylalanine,
18 (1*S*-*cis*)-*N*-[[3-[(Carboxymethyl)amino]carbonyl]-2,2,3-
19 trimethylcyclopentyl]carbonyl]-4-[(2,6-
20 dichlorobenzoyl)amino]-*L*-phenylalanine, and (1*S*-*cis*)-
21 *N*-[(3-Cyano-2,2,3-trimethylcyclopentyl)carbonyl]-4-
22 [(2,6-dichlorobenzoyl)amino]-*L*-phenylalanine.

1 15. A pharmaceutical composition comprising:
2 a therapeutically effective amount of the
3 compound as set forth in claim 1, 2, 3, 4, 5, 6, 7, 8,
4 9, 10, 11, 12, 13 or 14; and
5 a pharmaceutically acceptable carrier or diluent.

1 16. A method for treating or preventing $\alpha_4\beta_1$
2 adhesion mediated conditions in a human which
3 comprises administering to a patient an effective
4 amount of the compound according to claim 1, 2, 3, 4,
5 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14.

1 17. A method according to claim 16, wherein said
2 condition is selected from the group consisting of
3 rheumatoid arthritis, asthma, allergy conditions,
4 allograft rejection, psoriasis, eczema, contact
5 dermatitis and other skin inflammatory diseases,
6 inflammatory and immunoinflammatory conditions
7 including ophthalmic inflammatory conditions,
8 inflammatory bowel diseases, atherosclerosis, and
9 ulcerative colitis.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/13064

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C233/63 C07C233/87 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 22966 A (BIOGEN INC ;ADAMS STEVEN P (US); LIN KO CHUNG (US); LEE WEN CHERNG) 1 August 1996 see claims	1,15-17
A	K.TH. WANNER ET AL.: "Asymmetrische Synthesen mit chiralen 1,4-oxazin-2,5-dionen: Darstellung enantiomerenreiner 2-substituierter Pipecolinsäurederivate" LIEBIGS ANNALEN DER CHEMIE., vol. 5, 1993, pages 477-484, XP002079228 WEINHEIM DE see page 479; figure 3	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 October 1998

Date of mailing of the international search report

16/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5616 Patentaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Pauwels, G

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/13064

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16 and 17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/05135

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9736859 A	09-10-1997	AU 2536097 A	22-10-1997
WO 9535296 A	28-12-1995	AU 2682695 A	15-01-1996
		CA 2191979 A	28-12-1995
		CN 1151161 A	04-06-1997
		EP 0767790 A	16-04-1997
		JP 8319288 A	03-12-1996
WO 9622966 A	01-08-1996	AU 4911596 A	14-08-1996
		BG 101841 A	30-04-1998
		BR 9606778 A	06-01-1998
		CA 2211181 A	01-08-1996
		CN 1177343 A	25-03-1998
		CZ 9702340 A	18-03-1998
		EP 0805796 A	12-11-1997
		FI 973087 A	22-09-1997
		HU 9702461 A	28-04-1998
		NO 973384 A	19-09-1997
		PL 321848 A	22-12-1997
		SK 98797 A	04-02-1998
DE 19654483 A	02-01-1998	AU 3343097 A	21-01-1998
		WO 9800395 A	08-01-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

Indicate the Application No

PCT/US 98/13064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9622966 A	01-08-1996	AU 4911596 A	14-08-1996
		BG 101841 A	30-04-1998
		BR 9606778 A	06-01-1998
		CA 2211181 A	01-08-1996
		CN 1177343 A	25-03-1998
		CZ 9702340 A	18-03-1998
		EP 0805796 A	12-11-1997
		FI 973087 A	22-09-1997
		HU 9702461 A	28-04-1998
		NO 973384 A	19-09-1997
		PL 321848 A	22-12-1997
		SK 98797 A	04-02-1998